

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY
COMMITTEE (EMDAC) MEETING

Thursday, May 10, 2018

7:59 a.m. to 5:34 p.m.

Tommy Douglas Conference Center

10000 New Hampshire Avenue

Silver Spring, Maryland

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P R O C E E D I N G S

(7:59 a.m.)

Call to Order

Introduction of Committee

DR. WILSON: Good morning. Welcome to the EMDAC meeting. First, I would like to remind everyone to please silence your phones, pull out your phones, remember to silence it and any other devices if you've not already done so.

We have a variety of things to do as we start out here. First is identify the FDA press contact, Lauren Smith Dyer. Is Lauren here? She's in the back corner there.

So I'm Peter Wilson. I'm the chair of the Endocrinologic and Metabolic Drugs Advisory Committee and I'll be chairing the meeting, and we're now calling the meeting to order. We'll start by going around the table and each person will introduce himself or herself. And we'll start to the left here with FDA.

DR. THANH HAI: Good morning. I'm Dr. Thanh Hai. I'm an acting director in the Office of Drug

1 Evaluation II.

2 DR. SMITH: Good morning. I'm Jim Smith.
3 I'm deputy division director of Division of
4 Metabolism and Endocrinology Products.

5 DR. SHARRETTS: Good morning. I'm
6 John Sharretts. I'm acting clinical team leader in
7 the Division of Metabolism and Endocrinology
8 Products.

9 DR. ROBERTS: Morning. I'm Mary Roberts.
10 I'm the clinical reviewer for the Division of
11 Metabolism and Endocrinology Products.

12 DR. LaCIVITA: Good morning. My name is
13 Cynthia LaCivita. I'm the director for the
14 Division of Risk Management in the Office of
15 Surveillance and Epidemiology.

16 DR. SINCLAIR: Good morning. I'm
17 Susan Sinclair from the University of North
18 Carolina Wilmington. I'm an epidemiologist and I'm
19 in the clinical research program.

20 DR. NEATON: Jim Neaton, University of
21 Minnesota, biostatistician.

22 DR. EPSTEIN: Michael Epstein, private

1 practice, gastroenterologist and hepatologist in
2 Annapolis, Maryland, and I run a clinical research
3 program.

4 DR. LOW WANG: Cecilia Low Wang, University
5 of Colorado in Denver. I'm an endocrinologist.

6 DR. NEWMAN: Connie Newman. I'm from
7 New York University School of Medicine in New York.
8 I'm an endocrinologist with an interest in lipids
9 and cardiovascular disease.

10 DR. WEBER: Tom Weber, endocrinologist at
11 Duke University.

12 DR. STRONCEK: Dave Stroncek, hematologist
13 from the NIH Clinical Center, Bethesda, Maryland.

14 DR. EVERETT: Brendan Everett. I'm a
15 cardiologist at the Brigham and Women's Hospital in
16 Harvard Medical School in Boston.

17 DR. BONNER: Good morning. Latoya Bonner,
18 DFO for EMDAC.

19 DR. WILSON: Peter Wilson, preventive
20 cardiology, endocrinology, and lipidology at Emory
21 University.

22 DR. BUDNITZ: Dan Budnitz, epidemiologist

1 and medical officer, medication safety program at
2 CDC.

3 DR. MORRATO: Good morning, Elaine Morrato,
4 epidemiologist and also a professor in health
5 systems management and policy and associate dean
6 for public health practice at the Colorado School
7 of Public Health.

8 DR. BURMAN: Good morning. Ken Burman, a
9 professor of medicine at Georgetown University and
10 head of endocrine at MedStar Washington Hospital
11 Center.

12 MS. CUARESMA: Hi, good morning. I'm Nicole
13 Cuaresma. I'm a patient representative.

14 DR. SHAMBUREK: I'm Bob Shamburek. I run
15 the intramural NHLBI lipid clinic and I'm a
16 lipidologist and gastroenterologist.

17 DR. ORTEL: Good morning. Tom Ortel from
18 Duke, and I'm a hematologist specializing in
19 hemostasis and thrombosis.

20 DR. YANOVSKI: Susan Yanovski. I'm
21 co-director of the Office of Obesity Research at
22 the National Institute of Diabetes, Digestive, and

1 Kidney Diseases.

2 DR. RAUFMAN: Jean-Pierre Raufman. I'm
3 chair of the GI Drug Advisory Committee and chief
4 of gastroenterology at the University of Maryland.

5 DR. KANE: Good morning, Robert Kane. I'm a
6 hematologist.

7 DR. KEWALRAMANI: Good morning.
8 Reshma Kewalramani. I'm the chief medical officer
9 at Vertex and I'm the industry representative.

10 DR. WILSON: Thank you very much. So for
11 topics such as those being discussed at today's
12 meeting, there are often many varied opinions, some
13 of which are quite strongly held. Our goal is that
14 today's meeting will be a fair and open forum for
15 discussion of these issues, and that individuals
16 can express their views without interruption.

17 Thus, as a general reminder, individuals
18 will be allowed to speak into the record only if
19 recognized by the chair and we look forward to a
20 productive meeting using this method. In the
21 spirit of the Federal Advisory Committee Act and
22 the Government in the Sunshine Act, we ask that the

1 advisory committee members take care that their
2 conversations about the topics at hand take place
3 in the open forum of the meeting.

4 We are aware that members of the media are
5 anxious to speak with the FDA about these
6 proceedings. However, FDA will refrain from
7 discussing the details of this meeting with the
8 media until its conclusion. Also, the committee is
9 reminded to please refrain from discussing the
10 meeting topics during breaks or lunch. So thank
11 you. Now, over to Commander Latoya Bonner.

12 **Conflict of Interest Statement**

13 DR. BONNER: Good morning. The Food and
14 Drug Administration is convening today for the
15 meeting of the Endocrinologic and Metabolic Drugs
16 Advisory Committee under the authority of the
17 Federal Advisory Committee Act of 1972.

18 With the exception of the industry
19 representatives, all members and temporary voting
20 members of the committees are special government
21 employees or regular federal employees from other
22 agencies and are subject to federal conflict of

1 interest laws and regulations.

2 The following information on the status of
3 the committees' compliance with the federal ethics
4 and conflict of interest laws, covered by but not
5 limited to those found at 18 U.S.C. Section 208 is
6 being provided to participants in today's meeting
7 and to the public.

8 FDA has determined that members and
9 temporary voting members of these committees are in
10 compliance with the federal ethics and conflict of
11 interest laws.

12 Under 18 U.S.C., Section 208, Congress has
13 authorized FDA to grant waivers to special
14 government employees and regular federal employees
15 who have potential financial conflicts when it is
16 determined that the agency's need for a special
17 government employee's services outweighs his or her
18 potential financial conflict of interest or when
19 the interest of a regular federal employee is not
20 so substantial as to be deemed likely to affect the
21 integrity of the services which the government may
22 expect from the employee.

1 Related to the discussions at today's
2 meetings, members and temporary voting members of
3 the committees have been screened for potential
4 financial conflicts of interest of their own, as
5 well as those imputed to them, including those of
6 their spouses and minor children, and for purposes
7 of 18 U.S.C. Section 208, their employers.

8 These interests may include investments,
9 consulting, expert witness testimony, contracts,
10 grants, CRADAs, teaching, speaking, writing,
11 patents and royalties, and primary employment.

12 Today's agenda involves discussion of the
13 safety and efficacy of new drug application 210645
14 for volanesorsen solution for subcutaneous
15 injection, submitted by Akcea Therapeutics,
16 Incorporated.

17 The proposed indication is as an adjunct to
18 diet for the treatment of patients with familial
19 chylomicronemia syndrome.

20 This is a particular matters meeting during
21 which specific matters related to Akcea
22 Therapeutics's NDA will be discussed. Based on the

1 agenda for today's meeting and all financial
2 interests reported by the committee members and
3 temporary voting members, no conflict of interest
4 waivers have been issued in connection with this
5 meeting.

6 To ensure transparency, we encourage all
7 standing committee members and temporary voting
8 members to disclose any public statements that they
9 have made concerning the product at issue.

10 With respect to FDA's invited industry
11 representatives, we would like to disclose that
12 Dr. Reshma Kewalramani is participating in this
13 meeting as a non-voting industry representative
14 acting on behalf of regulated industry.

15 Dr. Kewalramani's role at this meeting is to
16 represent industry in general and not any
17 particular company. Dr. Kewalramani is employed by
18 Vertex Pharmaceuticals.

19 We would like to remind members and
20 temporary voting members that if the discussions
21 involve any other products or firms not already on
22 the agenda for which an FDA participant has a

1 personal or imputed financial interest, the
2 participants need to exclude themselves from such
3 involvement and their exclusion will be noted for
4 the record.

5 FDA encourages all other participants to
6 advise the committee of any financial relationships
7 that they may have with the firm at issue. Thank
8 you.

9 DR. WILSON: Thanks very much. So our next
10 step is we're going to proceed with the FDA's
11 introductory remarks from Dr. John Sharretts.

12 **FDA Introductory Remarks - John Sharretts**

13 DR. SHARRETTS: Good morning. My name is
14 John Sharretts. I am an acting clinical team
15 leader in the Division of Metabolism and
16 Endocrinology Products. Thank you for being here
17 today. We look forward to an informative
18 discussion.

19 The purpose of today's meeting is to discuss
20 the use of the drug volanesorsen as an adjunct to
21 diet for the treatment of hypertriglyceridemia in
22 patients with familial chylomicronemia syndrome or

1 FCS.

2 FCS comprises a group of autosomal recessive
3 disorders, characterized by the inability to
4 process dietary fats due to very low lipoprotein
5 lipase activity. Fat from the diet accumulates in
6 the form of chylomicron in the blood and these
7 chylomicrons contribute to very high triglyceride
8 levels.

9 Patients with FCS manifest characteristic
10 signs and symptoms such as recurrent acute
11 pancreatitis, abdominal pain, lipemia retinalis,
12 and eruptive cutaneous xanthomas. FCS is very
13 rare. The cited prevalence is 1 to 2 per million
14 and patients with FCS represent only a small
15 fraction of patients with severely elevated
16 triglycerides.

17 Other conditions such as diabetes or obesity
18 are far more likely to cause very severe
19 hypertriglyceridemia. This distinction is
20 important because patients with more common causes
21 of very high triglycerides may have very different
22 benefit-risk considerations from volanesorsen,

1 including alternate treatment options than patients
2 with FCS.

3 As you will learn later this morning, the
4 FDA review team generally agrees with the
5 applicant's major finding, that volanesorsen can
6 lower triglycerides substantially.

7 Changes in fasting triglycerides have been
8 used for many decades to support approval of drugs
9 intended to treat severe hypertriglyceridemia on
10 the assumption that TG lowering will decrease the
11 risk of acute pancreatitis.

12 A challenge with relying on a surrogate
13 endpoint, however, is that the magnitude of the
14 clinical benefit remains uncertain. Accordingly,
15 an estimate of volanesorsen treatment effect on
16 clinical outcomes, large or small, would help guide
17 the overall benefit-risk assessment.

18 To be clear, the purpose of this meeting is
19 not to re-adjudicate the use of triglycerides as a
20 surrogate for clinical endpoints, but instead to
21 discuss the benefits of volanesorsen specifically
22 in the intended population, considering the risks

1 of this drug.

2 If volanesorsen had a reassuring safety
3 profile, even a small clinical benefit associated
4 with the observed decrease in TG could lead to a
5 favorable benefit-risk assessment. With this
6 application, however, we are required to balance
7 the effect of volanesorsen on a surrogate endpoint
8 against substantial risk.

9 As you will learn, the review team has found
10 this assessment to be a considerable challenge.
11 Despite very intensive laboratory monitoring, some
12 patients treated with volanesorsen experienced
13 unpredictable rapid decreases in platelet counts
14 below 50,000 per microliter that, in some cases,
15 required hospitalization and additional treatment.

16 Drug-induced thrombocytopenia in this range
17 can be associated with serious or fatal bleeding
18 events. We are not reassured by the observation
19 that no serious or fatal bleeding event has
20 occurred to date because the development program
21 was small, as expected for evaluation of a rare
22 disease.

1 Furthermore, there was an increased risk for
2 bleeding related adverse events such as petechiae
3 and epistaxis with volanesorsen in the pivotal
4 trial. Our discussion therefore will ultimately
5 focus on the overall assessment of clinical benefit
6 and risk.

7 Today's speakers will consider the effect of
8 volanesorsen on clinically meaningful outcomes such
9 as abdominal pain and other symptoms that might be
10 important to patients with FCS as well as the
11 overall safety of the drug, including adverse
12 events other than thrombocytopenia.

13 Additionally, we will address the high rates
14 of drug discontinuation due to safety tolerability.
15 Drug discontinuation affects interpretation of the
16 clinical trials and impacts the potential effect
17 size in a real-world setting.

18 Now, we will turn to today's agenda. After
19 my introduction, the applicant will present to you
20 their view of the efficacy and safety of
21 volanesorsen followed by a series of presentations
22 by the FDA reviewers.

1 From the FDA, you will hear from Dr. Mary
2 Roberts, the clinical reviewer, Dr. Alex Cambon,
3 the statistical reviewer, Dr. Yunzhao Ren, the
4 clinical pharmacology reviewer, and Dr. Ingrid
5 Chapman, the risk management analyst.

6 You will have the opportunity to ask
7 clarifying questions following each set of
8 presentations. After that, we'll break for lunch
9 and return for the open public hearing. Then we'll
10 move on to the discussion points, which I would
11 like to introduce now.

12 The first discussion question addresses
13 volanesorsen's clinical benefit. Now, once again,
14 we are not asking you to readjudicate TG as a
15 surrogate endpoint. Instead, we would like to
16 understand your view of the benefits of this drug
17 for patients with FCS, including how the observed
18 TG-lowering effect informs labeling that includes a
19 proposed dosing strategy not studied in clinical
20 trials and the effect of drug discontinuation on
21 efficacy beyond 3 months.

22 Because the applicant has proposed labeling

1 claims regarding volanesorsen's effect on
2 pancreatitis and abdominal pain, we ask for your
3 assessment of those endpoints specifically.

4 Finally, we ask you to consider all the
5 efficacy data, both TG and clinical endpoints, to
6 characterize the overall magnitude of clinical
7 benefit.

8 Question 2 asks you to discuss the safety
9 and tolerability of volanesorsen, focusing on
10 adverse events other than thrombocytopenia and
11 bleeding, such as injection site reactions, immune-
12 related events such as serum sickness, and
13 hypersensitivity events such as anaphylaxis.

14 Question 3 addresses thrombocytopenia. This
15 discussion point asks you to describe your overall
16 concern for the risk of thrombocytopenia and
17 bleeding and your assessment of the adequacy of the
18 proposed monitoring strategy, the feasibility of
19 intensive monitoring on clinical practice and the
20 evidence to support the proposed dosing algorithm.

21 The fourth question asks you to consider the
22 intended population. This discussion point asks if

1 you believe that the term familial chylomicronemia
2 syndrome, without further definition, sufficiently
3 identifies the patient population for whom
4 volanesorsen may have a favorable benefit-risk
5 profile or whether you have alternative suggestions
6 to define the appropriate population.

7 Question 5 asks you to discuss whether you
8 think a risk evaluation and mitigation strategy or
9 REMS is necessary, whether it would be able to
10 ensure that the benefits outweigh the risks of
11 bleeding due to thrombocytopenia, and if you
12 recommend any changes if volanesorsen were to be
13 approved with a REMS.

14 Although you will hear the FDA proposal for
15 a REMS, you should not infer that FDA has already
16 determined that volanesorsen has a favorable
17 benefit-risk assessment to support approval with
18 such a REMS in place. Instead, the discussion
19 today is intended to inform our decision making.

20 Question 6 addresses the possibility that,
21 if the drug is approved, clinicians might use
22 volanesorsen in pediatric patients, who have not

1 been studied in the volanesorsen development
2 program. We would like to hear your level of
3 concern with respect to the potential use and your
4 recommendations for future study in this
5 population.

6 Finally, question 7 is a voting question,
7 which I will read verbatim. Based on the
8 information included in the briefing materials and
9 presented today, has the applicant provided
10 sufficient efficacy and safety data to support
11 approval of volanesorsen?

12 If yes, provide your rationale and any
13 recommendations regarding the indicated patient
14 population, dosing, clinical monitoring, risk
15 management strategies, and/or post-marketing
16 studies. If no, provide your rationale and comment
17 on what additional data would be required to
18 support approval.

19 I cannot emphasize enough that the details
20 of your comments and discussion following your vote
21 are as important if not more important in informing
22 our decision making than the vote tally itself.

1 With that, I will stop and turn the program back
2 over to the AC chair. Thank you again for joining
3 us for this important discussion.

4 DR. WILSON: Thanks very much. Both the
5 Food and Drug Administration and the public believe
6 in a transparent process for information gathering
7 and decision making. To ensure such transparency
8 at the advisory committee meeting, FDA believes
9 that it is important to understand the context of
10 an individual's presentation.

11 For this reason, FDA encourages all
12 participants, including the sponsor's non-employee
13 presenters, to advise the committee of any
14 financial relationships that they may have with the
15 firm at issue such as consulting fees, travel
16 expenses, honoraria, and interest in the sponsor,
17 including equity interests and those based upon the
18 outcome of the meeting.

19 Likewise, the FDA encourages you, at the
20 beginning of your statement, to advise the
21 committee if you do not have any such financial
22 relationships.

1 If you choose not to address this issue of
2 financial relationships at the beginning of your
3 presentation, it will not preclude you from
4 speaking. So now, we'll proceed with Akcea's
5 presentations.

6 **Applicant Presentation - Louis O'Dea**

7 DR. O'DEA: Good morning. I'm Louis O'Dea,
8 medical officer and head of regulatory affairs for
9 Akcea Therapeutics. We appreciate the opportunity
10 to present our data and I'd like to thank the
11 members of the committee for their commitment to
12 this process and for reviewing the pre-meeting
13 materials.

14 Today, we will discuss volanesorsen, a novel
15 antisense therapy that represents the first
16 effective treatment for patients with familial
17 chylomicronemia syndrome or FCS, a rare metabolic
18 disease with a high unmet medical need.

19 The cardinal feature of FCS is very high
20 plasma triglyceride levels, unresponsive to
21 available lipid-lowering therapies. While there
22 are many symptoms associated with the disease, the

1 major cause of morbidity and mortality is acute
2 pancreatitis, which can lead to multi-organ
3 failure, chronic pancreatitis, and even death.

4 Volanesorsen demonstrated significant
5 triglyceride reduction with decreases of more than
6 90 percent from baseline relative to placebo,
7 levels low enough to reduce the risk of
8 pancreatitis.

9 We've characterized the safety profile, in
10 particular related to the identified risk of
11 treatment-related thrombocytopenia. Importantly,
12 we developed a comprehensive risk management
13 program which will support patient safety and
14 continue to collect efficacy and safety data on a
15 long-term basis.

16 FCS has significant clinical consequences.
17 It is characterized by the presence of
18 chylomicrons, which are circulating in
19 triglyceride-rich particles, shown here as the
20 milky plasma in a blood sample.

21 Chylomicrons arise from normal digestion and
22 are typically metabolized through downstream lipids

1 to fatty acids. However, for patients lacking the
2 important enzyme to metabolized chylomicrons,
3 lipoprotein lipase, FCS is characterized by
4 persistent high levels of triglycerides, 10 to 30
5 times the upper limit of normal.

6 As you will hear from Dr. Rader, this
7 metabolic disorder causes a multitude of symptoms,
8 including recurrent abdominal pain, xanthomata, and
9 can have the serious and life-threatening
10 consequence of pancreatitis. Despite the severity
11 of FCS, there are currently no approved
12 pharmacologic agents to treat patients.

13 Existing drugs for hypertriglyceridemia are
14 not effective as they require functioning
15 lipoprotein lipase or LPL. Restrictive fat diet,
16 the first and essentially only current course of
17 treatment, also fails to adequately lower
18 triglycerides, as you will see in the baseline
19 triglyceride values of our study population.

20 Therefore, patients remain at risk for
21 pancreatitis and the other burdens of their
22 disease.

1 So let me describe what causes FCS and how
2 volanesorsen works in regards to the pathogenesis
3 of this disease. To understand the specific defect
4 that causes FCS, we must briefly consider the
5 origin and processing of triglycerides and
6 chylomicrons. Triglycerides arise from two
7 sources, internally from the formation of VLDL by
8 the liver and externally from food in the form of
9 chylomicrons.

10 Under normal circumstances, chylomicrons are
11 transient and metabolize by lipoprotein lipase and
12 the resulting triglycerides are processed to fatty
13 acids for use as fuel or to be stored for later
14 use.

15 apoC-III modulates the process by negatively
16 regulating lipoprotein lipase activity. Normal
17 plasma, when drawn, is clear. In patients with
18 FCS, lipoprotein lipase is defective. The
19 functional deficiency can arise from genetic
20 abnormalities in lipoprotein lipase itself or its
21 many regulatory elements.

22 In all cases, the final common pathway is

1 impaired lipoprotein lipase function, leading to
2 chylomicron accumulation. And this creates the
3 milky-appearing plasma, where we can measure
4 chylomicrons using standard tests for
5 triglycerides.

6 Our initial studies with volanesorsen
7 revealed an additional apoC-III-dependent
8 lipoprotein lipase-independent metabolic pathway
9 that's also involved in chylomicron clearance.
10 Inhibiting this pathway with volanesorsen, which
11 blocks apoC-III, facilitates chylomicron and
12 triglyceride metabolism.

13 Removing the break on chylomicron clearance
14 reduces their accumulation in patients with FCS.
15 Our approach is to use antisense technology to
16 block apoC-III production. Under normal
17 circumstances, apoC-III gene is transcribed to
18 messenger RNA and this messenger RNA is then
19 translated into apoC-III protein.

20 Antisense technology uses a complimentary
21 sequence to target the messenger RNA and this
22 messenger RNA is then translated into apoC-III

1 protein. Antisense technology uses a complimentary
2 sequence to target the messenger RNA of a target
3 protein for degradation, which blocks the process
4 and facilitates the clearance of the accumulated
5 chylomicrons.

6 The proposed indication for volanesorsen is
7 as an adjunct to diet for the treatment of adult
8 patients with familial chylomicronemia syndrome.
9 We're committed to treating only the small fraction
10 of patients diagnosed with FCS and these are the
11 patients who have the highest unmet medical need.

12 In regards to dosing, volanesorsen comes as
13 a single use pre-filled syringe of 300 milligrams
14 and is suitable for self-administration
15 subcutaneously. Our clinical trials used a
16 starting dose of 300 milligrams and included a
17 dose-adjustment paradigm. The proposed label
18 includes a similar paradigm, but one that
19 incorporates body weight as an additional
20 conservative basis for dose adjustment.

21 Volanesorsen's long half-life allows dosing
22 adjustment through dose frequency modification. As

1 part of our post-approval commitment, we're
2 proposing a comprehensive risk management program
3 with five important components that work together
4 to support patient safety and compliance. Our
5 labeling provides details regarding patient
6 selection, treatment, with instructions on dose
7 adjustments and platelet monitoring.

8 We're collaborating with the agency to
9 develop a risk evaluation and mitigation strategy,
10 with added elements to assure safe use. It will
11 include mandatory registration of all patients,
12 prescribers, and pharmacies. Distribution will be
13 controlled through specialty pharmacies, with
14 dispensing limited to a month's supply.

15 Enhanced pharmacovigilance will closely
16 monitor product use and assess long-term safety,
17 including identifying potential product risks and
18 the effectiveness of the risk management program.
19 We also plan to initiate a 5-year global treatment
20 registry study to prospectively collect additional
21 safety and efficacy data post-approval.

22 Supporting all of this is the patient

1 support program. Nurse case managers will
2 facilitate patient compliance and access to
3 platelet testing, including mobile testing and
4 compliance when away from home.

5 Our proposed integrated risk management
6 program will assure that only patients with FCS
7 will be treated with volanesorsen. Our commitment
8 includes multiple pathways to support compliance
9 and to ease the burden of monitoring patients and
10 physicians.

11 So with this short background in mind,
12 here's the agenda for the remainder of our
13 presentation. Dr. Dan Rader will discuss the
14 disease background and the diagnosis of FCS and the
15 need for a new therapy based on his experience
16 treating these patients.

17 Dr. Steven Freedman, an expert on
18 pancreatitis, will then describe triglyceride-
19 associated pancreatitis. I will return to present
20 the efficacy data from the clinical trials of
21 volanesorsen and Dr. Walter Singleton, the former
22 chief medical officer of Ionis, will discuss the

1 safety data.

2 Dr. Michael Stevenson, the head of medical
3 affairs at Akcea Therapeutics, will describe our
4 risk management program, including our proposed
5 REMS. Dr. Seth Baum, who treats patients with FCS
6 and has experience treating patients with
7 volanesorsen, will then close the presentation with
8 his clinical perspective.

9 We also have additional experts with us here
10 today. All experts have been compensated for their
11 time and travel to today's meeting. And so thank
12 you and, with that, I'll turn the presentation over
13 to Dr. Rader.

14 DR. WILSON: Dr. Rader, before you start, we
15 have a new member of our committee who has joined.
16 Would she please introduce herself? And we put
17 that into the record and where you are from.

18 MS. MCCOLLISTER-SLIPP: Hi, I'm actually not
19 Meghan Rowcliffe. I'm Anna McCollister-Slipp. I
20 just didn't see my name placard. I'm one of the
21 consumer representatives on the advisory committee.

22 DR. WILSON: Your name?

1 MS. MCCOLLISTER-SLIPP: It's Anna
2 McCollister-Slipp.

3 DR. WILSON: Thanks very much. We have a
4 chair for you to sit down here. So if you could
5 move down there --

6 MS. MCCOLLISTER-SLIPP: Thank you.

7 DR. WILSON: Thanks very much. We have yet
8 another one, a member of our committee. So would
9 you please take your chair, introduce yourself and
10 where you're from?

11 DR. ROWCLIFFE: Thank you. I'm Meghan
12 Rowcliffe. I'm a medication safety officer at
13 Johns Hopkins Hospital.

14 DR. WILSON: Thanks very much, Dr. Rader.
15 Go ahead.

16 **Applicant Presentation - Daniel Rader**

17 DR. RADER: Good morning. I'm Dan Rader,
18 professor of molecular medicine and chair of the
19 Department of Genetics at the University of
20 Pennsylvania.

21 I'm engaged in research involving the
22 genetics of lipid metabolism and a practicing

1 clinician focused on patients with genetic
2 disorders with lipid metabolism. Over the next few
3 minutes, I will review the characteristics of this
4 very rare disease and the impact that FCS has on
5 our patients.

6 Familial chylomicronemia syndrome or FCS is
7 an ultra rare serious metabolic disorder
8 characterized by extremely elevated chylomicrons
9 due to impaired chylomicron clearance.

10 Underlying causes of FCS include mutations
11 in the genes encoding lipoprotein lipase or LPL or
12 other LPL regulatory proteins that enable LPL
13 activity and effective chylomicron clearance.

14 FCS is characterized by severe
15 chylomicronemia, which is assessed by measuring
16 fasting triglycerides, as chylomicrons are not
17 routinely measured in clinical practice. Fasting
18 triglycerides above 750 milligrams per deciliter
19 are generally indicative of chylomicronemia.

20 One of the key consequences of FCS is
21 pancreatitis, which can be potentially life-
22 threatening and which you will hear more about from

1 Dr. Freedman.

2 Now, let's review the clinical presentation
3 of FCS. A key element of the FCS clinical
4 presentation is severe and persistent
5 hypertriglyceridemia which is refractory to
6 currently available lipid-lowering medications such
7 as fibrates and fish oils and a restricted fat
8 diet.

9 FCS often presents in childhood with severe
10 hypertriglyceridemia or pancreatitis, although
11 patients may be diagnosed at any age. A family
12 history of hypertriglyceridemia may be present,
13 though is not required for this autosomal recessive
14 genetic condition. There is often a history of
15 pancreatitis or unexplained abdominal pain.

16 Finally, the presence of secondary causes of
17 hypertriglyceridemia such as poorly controlled
18 diabetes, excessive alcohol use, or certain
19 medications makes the diagnosis of FCS less likely
20 and serves to help differentiate from other causes
21 of chylomicronemia.

22 The diagnosis of FCS has traditionally been

1 made clinically based on the clinical presentation
2 that I just reviewed. When FCS is suspected, the
3 clinical diagnosis can be supported by low post-
4 heparin plasma LPL activity of less than 20 percent
5 of normal.

6 However, this assay is not currently
7 available clinically outside the research setting.
8 Genetic testing for the identification of mutations
9 in genes involved in the LPL pathway can help
10 confirm the diagnosis.

11 These mutations may be homozygous, compound
12 heterozygous, or rarely double heterozygous
13 involving two different genes. However, it is
14 likely that additional genes may cause FCS and
15 therefore negative genetic testing does not exclude
16 the diagnosis of FCS.

17 Patients with FCS represent a very small
18 subgroup of those with elevated triglyceride
19 levels. To contextualize the rarity of FCS, this
20 figure shows the distribution of
21 hypertriglyceridemia in the general population.

22 Starting from the bottom of this pyramid,

1 normal, fasting triglycerides are considered to be
2 less than 150 milligram per deciliter and
3 constitute the majority of the general population.

4 Approximately 28 percent of the population
5 have fasting triglycerides greater than 150
6 milligram per deciliter, which are generally
7 considered to be elevated. Those with
8 chylomicronemia, that is, a measured triglyceride
9 level in excess of 750 milligram per deciliter,
10 represent only approximately 0.1 percent of the
11 general population.

12 Importantly, the majority of these patients
13 have obesity, uncontrolled diabetes, excessive
14 alcohol use, or other medications known to elevate
15 triglyceride levels. These patients also generally
16 have at least some response to triglyceride-
17 lowering therapy.

18 Importantly, patients with FCS represent
19 only a minor fraction of patients with
20 chylomicronemia. In contrast to the broader group,
21 patients with FCS have persistent triglycerides
22 greater than 750, are absent of secondary causes,

1 and are not responsive to triglyceride-lowering
2 therapies, indicating that they have low LPL
3 activity.

4 While the true prevalence of FCS has not
5 been systematically evaluated, the best estimates
6 suggest that it is approximately 1 to 4 patients
7 with FCS per 1 million individuals. This is the
8 well-defined ultra rare group of patients with the
9 highest unmet medical need that we're focusing on
10 today.

11 Because the complications of FCS are due to
12 chylomicronemia, triglyceride reduction is the main
13 goal of therapy in patients with FCS. The major
14 treatment goal in FCS includes reduction of
15 pancreatitis risk.

16 Another goal of treatment is the reduction
17 in the other symptoms and associated disease burden
18 in this condition. Chylomicron lowering is
19 assessed through reduction in fasting triglyceride
20 levels.

21 As Dr. Freedman will present, pancreatitis
22 risk correlates with triglyceride levels; the

1 higher the triglyceride, the higher the risk of
2 pancreatitis. A substantial reduction in
3 triglycerides is expected to decrease the risk of
4 pancreatitis.

5 Unfortunately, there are no effective
6 therapeutic interventions for patients with FCS.
7 Patients with FCS are generally refractory to
8 triglyceride-lowering medications such as fibrates
9 and fish oils. This is due to the fact that these
10 drugs are in part dependent on functional LPL and
11 therefore lack of response to these drugs serves as
12 a surrogate for low LPL activity.

13 The standard of care for FCS consists of
14 extreme dietary fat restriction to less than 20
15 grams of fat per day, the equivalent of
16 approximately 1 tablespoon of olive oil or half of
17 an avocado and also avoidance of alcohol.

18 Even with strict adherence to this
19 challenging regimen, triglyceride levels are not
20 typically lowered sufficiently to reduce the risk
21 of pancreatitis in many patients, leaving
22 individuals at risk for pancreatitis and other

1 signs and symptoms of this disease.

2 To summarize, FCS is an ultra rare inherited
3 life-threatening metabolic disorder of triglyceride
4 metabolism. FCS can be clinically differentiated
5 from the larger group of patients with
6 chylomicronemia. Currently, there are no effective
7 therapies for lowering triglyceride levels in
8 patients with FCS.

9 As a result, most patients with FCS remain
10 at high risk for pancreatitis. Thus patients with
11 FCS have a clear unmet need for effective and
12 sustained triglyceride-lowering treatments to
13 reduce the disease burden.

14 In view of the high risk and severity of
15 pancreatitis in patients with FCS, Dr. Freedman
16 will expand on this potentially life-threatening
17 consequence. Thank you.

18 **Applicant Presentation - Steve Freedman**

19 DR. FREEDMAN: Good morning. My name is
20 Dr. Steve Freedman. I'm professor of medicine at
21 Harvard Medical School and director of the Pancreas
22 Center at Beth Israel Deaconess Medical Center in

1 Boston, one of the largest pancreatic referral
2 centers in North America.

3 I treat patients of all ages with
4 pancreatitis caused by hypertriglyceridemia as well
5 as cystic fibrosis, as I'm also affiliated with
6 Boston Children's Hospital. I'm here today to
7 provide additional insights into
8 hypertriglyceridemia-induced pancreatitis as it
9 pertains to FCS.

10 Approximately 70 percent of patients with
11 FCS will develop pancreatitis as a result of their
12 chylomicronemia, hypertriglyceridemia, with half of
13 these individuals having anywhere from 2 to 96
14 episodes in their lifetime. In addition, the
15 morbidity and mortality of pancreatitis associated
16 with hypertriglyceridemia is greater than from
17 other etiologies.

18 Correlation between increased triglyceride
19 levels and the increased risk of pancreatitis is
20 well established. Therefore, one of the major
21 goals for patients with FCS is to reduce their
22 triglyceride level in order to reduce the

1 associated risk of pancreatitis.

2 Since there's little information on
3 pancreatitis in FCS due to the rarity of this
4 disease, I'll focus the majority of this
5 presentation on the data from patients with severe
6 hypertriglyceridemia. I'll begin with a brief
7 overview of pancreatitis and then discuss the
8 relationship to triglyceride levels.

9 Pancreatitis is a serious and potentially
10 life-threatening condition. It's characterize by
11 severe upper abdominal pain with nausea, vomiting,
12 and fever. It's usually an acute event, but with
13 repeated bouts, chronic pancreatitis can occur,
14 which is an unrelenting, searing, daily pain that
15 worsens with every meal.

16 Mild cases resolve within 2 to 4 days, but
17 in approximately 20 percent of patients,
18 complications develop as a result of necrotizing
19 pancreatitis, leading to multiorgan failure, which
20 consists of acute respiratory distress syndrome,
21 renal failure, and/or shock.

22 In addition, infection can develop and

1 pseudocysts may form over time. Mortality can be
2 quite high, ranging from about 3 percent in milder
3 cases to 30 percent in severe cases. The risk of
4 pancreatitis as well as severity increases along a
5 continuum of increasing triglyceride levels.

6 Shown here are data from a U.S. claims
7 database review of over 40,000 adults with
8 triglyceride levels above 500 milligrams per
9 deciliter. The incidence of pancreatitis over an
10 average 825-day observation period is shown as a
11 function of follow-up triglyceride levels.

12 The analysis shows that the risk of acute
13 pancreatitis increases proportionally with
14 increasing triglyceride levels. Importantly, this
15 study showed that lowering triglycerides from the
16 starting value of greater than 500 could reduce the
17 pancreatitis risk.

18 If we examine this risk at higher
19 triglyceride levels, other studies have shown that
20 triglyceride values above 1,000 milligrams per
21 deciliter, approximately 5 percent of individuals
22 will develop acute pancreatitis over their

1 lifetime.

2 This increases to 10 to 20 percent with
3 triglyceride values above 2,000. Conversely,
4 reducing triglycerides decreases the risk of
5 pancreatitis. In general, the recommendations are
6 to reduce triglyceride levels below 1,000
7 milligrams per deciliter to reduce the risk.

8 So now, let's look at the severity of
9 pancreatitis as a function of triglyceride levels.
10 Nawaz and colleagues conducted a prospective
11 observational study evaluating outcomes in 201
12 patients hospitalized with acute pancreatitis, with
13 serum triglyceride levels measured within the first
14 72 hours of admission.

15 Shown here is the proportion of patients
16 with organ failure as a function of initial
17 triglyceride level, multi-organ failure persisting
18 beyond 48 hours defines severe pancreatitis in the
19 Atlanta criteria and is the most common cause of
20 death in these patients.

21 As you can see, there's a clear
22 concentration-dependent relationship between

1 triglyceride levels and persistent organ failure.
2 Nearly half of the patients with triglyceride
3 values greater than 1,000 had organ failure in this
4 study.

5 Additional data from the Nawaz study
6 confirmed that higher triglyceride levels are
7 associated with more severe disease. 60 percent of
8 patients with very high triglyceride values needed
9 to be in the ICU compared to 23 percent with normal
10 triglyceride values.

11 Fifty percent of patients with triglyceride
12 over 1,000 had necrosis and had a prolonged
13 hospital stay. Mortality in this study was 8
14 percent compared to 3 percent with normal
15 triglyceride values on admission.

16 That's the patient's first hospitalization
17 for hypertriglyceridemia-induced pancreatitis,
18 maybe their last due to death.

19 In closing, pancreatitis due to underlying
20 hypertriglyceridemia is a much more severe form of
21 pancreatitis as compared to other etiologies. Both
22 the morbidity, including multiorgan failure and

1 mortality, are increased.

2 Among the many clinical manifestations of
3 FCS, pancreatitis is the most serious.
4 Unfortunately, even the first instance of
5 pancreatitis may be fatal. The suffering of these
6 patients cannot be estimated when meals are a
7 frequent trigger of abdominal pain and patients
8 live in constant fear that one of these bouts will
9 put them in the hospital and likely in the
10 intensive care unit.

11 Unfortunately, this is a typical scenario
12 for these patients. All available data indicate
13 that the risk of pancreatitis increases and
14 decreases as a continuum related to triglyceride
15 levels. Therefore, an effective medication to
16 substantially lower triglycerides would allow
17 patients to achieve triglyceride levels below those
18 associated with an elevated pancreatitis risk.
19 Thank you. I'll now return the podium to
20 Dr. O'Dea.

21 **Applicant Presentation - Louis O'Dea**

22 DR. O'DEA: Thank you, Dr. Freedman. I'd

1 like to discuss the efficacy data supporting the
2 application of volanesorsen in this proposed
3 indication. The data show that patients treated
4 with volanesorsen achieved statistically
5 significant and clinically meaningful sustained
6 reductions in fasting triglyceride levels.

7 Importantly, this efficacy was consistent
8 across clinical studies. Here is an overview of
9 the volanesorsen clinical development program. For
10 an ultra rare disease, this is a sizeable dataset
11 of almost 400 patients and subjects, of whom
12 312 received volanesorsen and 84 of these were
13 patients with FCS.

14 This is the largest collection of clinical
15 data in patients with FCS to date. The program
16 supporting the application includes 2 phase 1
17 studies conducted in healthy volunteers and 2 phase
18 2 studies conducted in patients with
19 hypertriglyceridemia.

20 The primary data for the FCS indication are
21 based on the phase 3 study CS6, which will be the
22 focus of today's presentation. Study CS7, an open-

1 label extension study in patients with FCS,
2 provides further information on long-term
3 triglyceride reductions. Patients with FCS in this
4 study rolled over from CS6, or study CS16, or were
5 recruited as naïve patients.

6 CS16 provides further efficacy and safety
7 data of volanesorsen for triglyceride reduction in
8 severely hypertriglyceridemic patients and also on
9 pancreatitis risk reduction.

10 These patients allowed for increased
11 exposure that would not be possible if we studied
12 patients with FCS alone due to the ultra rare
13 nature of this disease.

14 Let me start by briefly describing our dose-
15 finding studies, CS2. CS2 was a phase 2 placebo-
16 controlled dose-response study conducted in 85
17 moderately hypertriglyceridemic subjects to
18 evaluate the effects of volanesorsen on fasting
19 apoC-III and on triglyceride levels.

20 We studied three doses, 100, 200, and 300
21 milligrams. And patients were required to have
22 baseline triglyceride levels between 440 and

1 2,000 milligrams per deciliter. The study included
2 patients on volanesorsen alone and a cohort of
3 patients taking fibrates.

4 Finally, 3 genetically confirmed patients
5 with FCS were enrolled in the study and received
6 300 milligrams of volanesorsen for 3 months. This
7 study demonstrated a clearer dose-dependent
8 reduction in triglycerides. Here, you see placebo
9 in orange compared to the three tested doses of
10 volanesorsen with dosing going through day 85, as
11 shown in the shaded area.

12 At baseline, the mean triglyceride level was
13 581 milligrams per deciliter. At 3 months,
14 volanesorsen, 300 milligrams, achieved an
15 80 percent reduction in fasting apoC-III and, as
16 you can see, a 71 percent mean reduction in
17 triglycerides.

18 The effect was sustained for at least
19 another 3 months. After dosing stopped,
20 triglyceride levels slowly returned to baseline,
21 reflecting the long effective half-life of
22 volanesorsen.

1 Among the 3 patients with FCS studied with
2 volanesorsen, the triglyceride reduction at
3 3 months was 64 percent.

4 Therefore, this study showed clinically
5 meaningful reductions in triglyceride with 300
6 milligrams of volanesorsen. In addition, it
7 confirmed that the apoC-III pathway was a target
8 for the treatment of patients with FCS who have
9 similar degrees of triglyceride reduction as normal
10 subjects.

11 Study CS2 identified no dose-limiting
12 toxicities. And while some dose-dependent platelet
13 reductions were observed, the group mean values
14 remained within the normal range. No platelet-
15 related serious adverse events or discontinuations
16 occurred.

17 This safety profile supported taking the
18 300-milligram dose into our phase 3 development
19 program, in particular considering the extreme
20 elevations of triglycerides in patients with FCS.

21 Let's now review our pivotal phase 3 study,
22 CS6, conducted in patients with FCS. CS6 was a

1 phase 3 double-blind randomized placebo-controlled
2 12-month study. The study comprised a screening
3 period of up to 8 weeks, which included a diet
4 stabilization period of at least 6 weeks.

5 Subsequently, patients were randomized 1:1
6 to receive subcutaneous injections of either
7 volanesorsen, 300 milligrams, once weekly or a
8 matching volume of placebo. Following completion
9 of the 52-week treatment phase, patients could
10 elect to enroll in the open-label extension study,
11 CS7. Patients not participating in the open-label
12 extension entered a 13-week post-treatment follow-
13 up period.

14 Inclusion criteria required that patients be
15 18 years of age or older and to have agreed to a
16 very restrictive fat diet of 20 grams or more per
17 day, which is the current standard of care.

18 Patients were also required to have a
19 fasting triglyceride of greater than or equal to
20 750 milligrams per deciliter and to have either
21 positive genetic or lipoprotein lipase functional
22 testing, documented pre-randomization.

1 Most patients were also retested for genetic
2 markers on study. This is the population for which
3 we are pursuing approval. Finally, a majority of
4 patients were to have prior pancreatitis.

5 The agreed-upon primary endpoint in study
6 CS6 was the percent change in fasting triglyceride
7 levels from baseline to 3 months, which is
8 sufficient to realize the full effect of
9 triglyceride-lowering therapies.

10 All triglyceride endpoints are based on two
11 values, separated by 1 week. The full analysis set
12 included all patients who were randomized, received
13 at least 1 dose of study drug, and had a baseline
14 plasma triglyceride assessment.

15 Various imputation methods were used for
16 missing data. We minimized missing data by asking
17 that patients continue to attend scheduled study
18 milestone visits even if they discontinued study
19 medication.

20 Patients who discontinued early were also
21 followed for safety, including cases of
22 pancreatitis, achieving similar durations of

1 observation for both volanesorsen and placebo
2 groups. That said, all patients had triglyceride
3 values at month 3, so the primary endpoint retained
4 the full analysis set with all observed values.

5 Imputation methods for months 6 and 12 again
6 included multiple imputations methods as well as a
7 post hoc analysis of missing not at random.

8 So turning to our study demographics, these
9 study demographics were balanced between arms.
10 Patient population was relatively young with an age
11 range of 20 to 75. Patients were diagnosed on
12 average at age 27. The genders were approximately
13 equally represented in each arm and patients had a
14 BMI of around 25.

15 Their body weight was 70 kilos on average
16 and the majority of patients were white. Baseline
17 mean triglyceride levels were markedly elevated
18 with mean levels around 2,200 milligrams per
19 deciliter, close to 20 times the normal value.

20 It's important to remember that these
21 baseline values reflect levels even after 6 to
22 8 weeks of diet control and education. More than

1 90 percent of patients had triglyceride values
2 greater than 750 at study start.

3 Per the entry criteria, FCS diagnosis was
4 confirmed genetically or by a lipoprotein lipase
5 assay. As expected, most patients had a history of
6 acute pancreatitis. 29 percent of patients were
7 also on lipid-lowering agents and still had very
8 high levels of triglycerides.

9 In study CS6, 58 percent of volanesorsen-
10 treated patients and 94 percent of placebo-treated
11 patients completed 12 months of study treatment.
12 14 patients discontinued treatment with
13 volanesorsen. 4 of these were voluntary
14 withdrawals. 9 were related to adverse events.
15 5 of these in turn were adverse events of platelet
16 count reductions.

17 Moving to the primary results, study CS6 met
18 its primary endpoint of percent reduction in
19 triglycerides at 3 months compared to placebo.
20 Volanesorsen-treated patients achieved a mean
21 reduction in triglycerides of 94 percent compared
22 to placebo and 77 percent compared to their own

1 baseline.

2 This is statistically significant when
3 compared to placebo. This result reflects a mean
4 reduction in triglycerides of about
5 1,600 milligrams per deciliter from baseline and
6 brings patients to a new average of 590 milligrams
7 per deciliter at month 3.

8 So next, we'll present the results of the
9 primary endpoint by individual patient. The X axis
10 represents individual patients from study CS6. The
11 Y axis shows triglyceride values. The horizontal
12 line at 750 represents the triglyceride level at
13 which chylomicrons form in the blood and therefore
14 are responder threshold.

15 Let me walk you through the results of
16 1 patient before presenting all data. The blue
17 circle represents the baseline triglyceride value
18 of 3,690 for this patient. At month 3, this
19 patient's triglycerides were reduced to
20 460 milligrams per deciliter.

21 Here are the rest of the results from the
22 volanesorsen-treated patients, ordered based on

1 final triglyceride values. By month 3, all
2 patients had a decrease in triglycerides from
3 baseline and 77 percent of the patients achieved
4 triglyceride values below 750.

5 The data in orange represent the placebo,
6 with changes in both directions from baseline
7 values. A notable difference between treatment
8 groups underscores both the pronounced efficacy and
9 the high response rate to volanesorsen.

10 So moving to the secondary endpoint results,
11 as Dr. Freedman stated, there are risk thresholds
12 for the serious complications of FCS. Consistent
13 with previous FCS development programs, 750
14 milligrams per deciliter was pre-specified as the
15 responder threshold, as it represents an important
16 risk threshold for pancreatitis and reflects the
17 triglyceride level at which chylomicrons
18 predominate in the circulation.

19 Seventy-seven percent of treated patients
20 achieved that level compared to 10 percent of
21 placebo patients. We also evaluated other risk
22 thresholds commonly found in the literature;

1 1,000 milligrams per deciliter, 880 milligrams per
2 deciliter, which is more widely applied in Europe,
3 and 500 milligrams per deciliter, which is an
4 important level for risk of pancreatitis since it
5 represents a 2.5-fold risk for patients with normal
6 triglyceride values.

7 Independent of the threshold assessed,
8 patients treated with volanesorsen achieved a
9 statistically significant reduction in risk levels.

10 So moving to long-term efficacy data, we
11 continue to see clinically meaningful and
12 statistically significant reductions in
13 triglycerides at the pre-specified 6- and 12-month
14 time points. These data include all 33 patients in
15 the full analysis set at each time point, with a
16 multiple imputation method use for missing data at
17 6 and 12 months.

18 This means that, even if patients
19 discontinued early or went off treatment after
20 month 3, a value was imputed at months 6 and 12.
21 As a reminder, dose adjustments were made after
22 month 3 if needed to minimize platelet count

1 reductions.

2 To illustrate the contribution of these
3 reductions or discontinuations, let me turn to the
4 next slide. This graphic provides detail on
5 persistence of efficacy, taking into account dose
6 adjustments. As you can see, patients who
7 continued without dose adjustment show consistent
8 sustained response to volanesorsen.

9 Patients who had a dose adjustment retained
10 most of the triglyceride reductions through 52
11 weeks. Patients who discontinued prematurely
12 contributed to some loss of efficacy within the
13 full analysis set at 52 weeks.

14 As expected, the placebo group showed no
15 overall improvement over time. It's important to
16 note that, for patients who completed 52 weeks,
17 significant triglyceride reduction was maintained.

18 Using this dataset, we evaluated factors
19 that might predict the need for dose adjustment,
20 body weight was the strongest predictor, leading us
21 to propose weight-based dose adjustment post-
22 approval.

1 Moving to the pre-specified secondary
2 endpoint of maximum intensity of abdominal pain, it
3 was not a significant difference between treatment
4 groups and reported events nor in the distribution
5 of event severity. Abdominal pain is an important
6 part of FCS and is confirmed by patient surveys.

7 Our phase 3 study finding likely reflects
8 limitations of the measurement tool that we use.
9 So we're working to develop a more appropriate
10 validated pain assessment tool for patients with
11 FCS.

12 So next, I'll turn to additional pre-
13 specified exploratory endpoints. Pancreatitis, in
14 association with abdominal pain, was a pre-
15 specified endpoint in the study protocol and
16 statistical plan. In the absence of an effect on
17 pain, we looked at events of pancreatitis alone.

18 Serious adverse events of pancreatitis were
19 adjudicated by an independent medical committee.
20 On treatment, 1 volanesorsen-treated patient
21 suffered an event of pancreatitis and 3 placebo-
22 treated patients suffered 4 events of pancreatitis.

1 So in such a rare disease with small patient
2 numbers and the reported background frequency of
3 pancreatitis, the significant impact on
4 pancreatitis would not have been predicted.
5 Nonetheless, these numbers do suggest a therapeutic
6 effect.

7 An additional exploratory analysis looked at
8 patients with more than one event of pancreatitis
9 in the past 5 years. We noted that patients may
10 expect an attack of pancreatitis every 4 to 5
11 years. So we looked at patients with more than
12 these frequency to ascertain if volanesorsen has a
13 protective effect.

14 There were 24 events in 7 volanesorsen
15 patients over the 5 years prior to the study and
16 none of these patients experienced pancreatitis
17 during the course of treatment. Among the placebo
18 patients, there were 17 prior events and
19 4 patients.

20 By contrast, to the improvement seen on
21 volanesorsen, 3 placebo patients experienced
22 4 events of pancreatitis during the study period.

1 In the absence of a validated tool, quality of life
2 tool for patients with FCS, we use two general
3 questionnaires, the EQ-5D and the SF-36.

4 While these tools are commonly used in
5 clinical trials, they've not been validated for
6 patients with FCS. No differences were observed in
7 the quality of life between drug- and placebo-
8 treated patients used in these measures.

9 So we understand that enhancing the quality
10 of life for patients with FCS is an essential
11 component in managing the disease. And therefore,
12 we have been committed to develop an FCS-specific
13 quality of life measure from early on in this
14 program.

15 Our early work has been published and has
16 become a reference in the field. Further data I'd
17 like to briefly review are from the open-label
18 extension study, CS7. This study is a phase 3
19 open-label clinical trial designed to evaluate both
20 the safety and efficacy of extended treatment with
21 volanesorsen in patients with FCS.

22 Patients in CS7 included continuing

1 volanesorsen-treated patients from studies CS6 and
2 CS16 as well as treatment-naïve patients made up of
3 placebo patients from these studies and newly
4 identified patients with FCS. The majority of
5 eligible patients chose to continue treatment.

6 New patients with FCS who had not
7 participated in CS6 or CS16 had to meet the
8 eligibility criteria of CS6 to be enrolled. CS7
9 allowed treatment for up to 24 months after the
10 initial 12 months in study CS6.

11 Let's look at the sustainability of effect
12 for patients moving from CS6 to CS7. Volanesorsen
13 treatment continues to provide efficacy for at
14 least 24 months as patients from CS6 progress into
15 CS7. We present here the longitudinal data of CS7
16 with the 12 months of earlier participation in
17 study CS6 shown in the shaded area.

18 The CS7 study continues, but these data are
19 taken from the last formal analysis and therefore
20 not all current patients are included in the later
21 time points.

22 I'll now briefly walk through the additional

1 data which are derived from study CS16 in patients
2 with severe hypertriglyceridemia. Although we are
3 not seeking an indication for patients with severe
4 hypertriglyceridemia, the triglyceride levels in
5 this population are well above the upper limit of
6 normal while on standard treatment.

7 We therefore consider patients with severe
8 hypertriglyceridemia to be a relevant population to
9 better understand the safety and pharmacology of
10 volanesorsen, in particular since as Dr. Freedman
11 indicated they have an increased background risk of
12 pancreatitis.

13 In study CS16, volanesorsen caused
14 significantly greater triglyceride reductions in
15 the volanesorsen group relative to placebo. The
16 difference from placebo and percent change in
17 triglycerides was 71 percent, consistent with the
18 efficacy observed in patients with FCS.

19 Adjudicated pancreatitis events occurred in
20 3 patients in the placebo group compared with no
21 patients in the volanesorsen group.

22 To further evaluate the potential effect on

1 the risk of pancreatitis, we conducted informative
2 post hoc analyses of all patients with FCS and
3 patients with hypertriglyceridemia. Among patients
4 with FCS from study CS6 and study CS16, we observed
5 similar distributions of pancreatitis events.

6 Overall, there were 6 events in 4 placebo
7 patients and 1 event in a volanesorsen patient.
8 Each individual study and the group of all patients
9 with FCS from both studies show point estimates for
10 risk of pancreatitis well below 1.

11 Importantly, the results from the FCS and
12 hypertriglyceridemic populations were consistent.
13 So to conclude, volanesorsen treatment leads to
14 clinically meaningful and statistically significant
15 reductions in triglycerides of 94 percent relative
16 to placebo. These reductions in triglycerides were
17 sustained over time.

18 The degree of triglyceride reduction should
19 reduce the risk of pancreatitis and point estimates
20 for pancreatitis risk support this potential. In
21 fact, in all exploratory assessments of
22 pancreatitis, volanesorsen consistently showed a

1 numeric benefit.

2 Given the severity of this disease and the
3 absence of alternative effective therapy, these
4 substantial reductions in triglycerides, which
5 drive the symptoms and complications of this
6 disease are meaningful and medically important to
7 these patients.

8 Overall, these data indicate that
9 volanesorsen could be the first effective therapy
10 to treat patients with FCS. So with that, I'll
11 turn the podium over to my colleague, Dr. Walter
12 Singleton, who's been involved in this program
13 since its inception.

14 **Applicant Presentation - Walter Singleton**

15 DR. SINGLETON: Thank you, Dr. O'Dea. I'm
16 Walter Singleton, former chief medical officer for
17 Ionis Pharmaceuticals. Our data demonstrate that
18 the safety profile of volanesorsen is well
19 understood with risks that could be monitored and
20 managed.

21 So let me start by reviewing the
22 volanesorsen exposure throughout out our phase 2

1 and phase 3 programs. The clinical trial program
2 included 189 patients who received treatment with
3 the 300-milligram dose of volanesorsen at the time
4 of data cut-off for this review.

5 And these totals include patients on
6 volanesorsen in the controlled phase 2 and 3
7 studies, patients on placebo in the controlled
8 trials who then went on to receive volanesorsen in
9 the open-label extension study, CS7, and a small
10 number of new patients entering CS7 de novo.
11 150 of these patients were treated for at least
12 3 months, 74 for 6 months or more, and 26 for more
13 than a year.

14 Of these, 84 are patients with familial
15 chylomicronemia syndrome, with the majority from
16 the pivotal CS6 study. And of these, 48 have been
17 treated for 6 months or longer and 26 for over a
18 year at the time of data cut-off. So as you will
19 appreciate, this represents a substantial database
20 for a study in such a rare population.

21 These data are from the pivotal study CS6 in
22 patients with FCS. Together with supporting data

1 from CS6 to provide a larger safety dataset. The
2 numbers of adverse events were similar between
3 active treatment and placebo groups.

4 In CS6, there were 7 of 33 patients who had
5 a serious adverse event in the volanesorsen arm and
6 5 of 33 in the placebo arm. And there were no
7 deaths across the studies.

8 The overall rate of discontinuation was in
9 the range of 20 to 27 percent in patients on
10 volanesorsen and between 0 and 8 percent in
11 patients on placebo.

12 The most common reason for discontinuation
13 in CS6 was platelet count decrease from
14 thrombocytopenia. In addition, 2 patients also
15 discontinued due to fatigue and one to injection
16 site reaction.

17 The most common reason for discontinuation
18 for CS16 was injection site events, but all
19 patients who discontinued due to injection site
20 events had events that were moderate in severity
21 and all the other events which still occurred in a
22 single patient in each study group.

1 So I would now like to focus the rest of
2 this presentation on specific safety topics,
3 including platelet count reductions, injection site
4 reactions, immunogenicity, and renal and hepatic
5 events.

6 So first focusing on platelet changes, the
7 first thing to note is that 55 percent of patients
8 with FCS and CS6 on volanesorsen, 18 were less than
9 100,000 per cubic millimeter on treatment versus
10 none on placebo. In CS16, 9 of the 75 patients
11 with volanesorsen had a platelet count below 100
12 compared with 1 of 38 patients in the placebo
13 group.

14 However, breaking these into severity
15 categories, it's clear that the more severe
16 reductions in both studies were observed only in
17 the volanesorsen-treated patients with 2 patients
18 with FCS dropping below 25,000.

19 Now, this graph shows mean platelet count by
20 patient study week. At the start of the CS6 study,
21 based on phase 2 data, platelets were monitored
22 every six weeks. Now, changes in platelet count in

1 most volanesorsen patients were gradual declines
2 and stabilized over time, with platelet count
3 generally remaining above 100,000.

4 Severe thrombocytopenia, however, occurred
5 in 3 patients, shown here in the red triangles.
6 And you will note that the latter two events
7 occurred in May of 2016, within a three-day period.
8 And this is what triggered the enhanced monitoring
9 that you'll hear about later.

10 All 3 cases of severe thrombocytopenia
11 occurred on the original protocol monitoring of
12 every 6 weeks. And as a result of this, the
13 algorithm was revised to increase monitoring to
14 every 2 weeks in order to identify potential
15 platelet reductions at the earliest possible stage.

16 Over the course of the entire clinical
17 program, 9 patients had platelet count reductions
18 below 50,000 per cubic millimeter. It's important
19 to note that all patients shown here recovered and
20 there were no major bleeding events.

21 Four of these patients had reductions in
22 platelet monitoring even after the enhanced

1 monitoring program had been implemented. And in
2 3 of the 4 events, either the monitoring interval
3 or dose adjustment were not carried out in
4 accordance with the algorithm.

5 We investigated all these events and
6 considered the causes when improving our algorithm
7 and designing our risk management program.

8 For platelet reductions that occurred during
9 the enhanced monitoring, treatment was immediately
10 discontinued. Platelet levels recovered out of the
11 higher risk zone in between 3 and 6 days and
12 returned to normal in approximately 2 weeks or
13 less.

14 As is the case with many medications given
15 by subcutaneous injection, adverse events at the
16 injection site are frequent and as shown here are
17 seen in both groups. The majority of these adverse
18 events were mild. None were severe. And
19 importantly, they led to discontinuation in only 1
20 patient with FCS in the CS6 study and the incidence
21 appeared to decrease over time.

22 Turning now to immunogenicity, overall,

1 antidrug antibodies were detected in 11 CS6
2 patients on volanesorsen and in 1 placebo patient.
3 The median time to onset of antibodies with 180
4 days. And these were generally present at low
5 titers.

6 Importantly, triglyceride reductions were
7 similar between antidrug antibody positive and
8 negative patients. And there was no association
9 between antidrug antibody status and the incidence
10 of injection site reactions, constitutional
11 symptoms, or platelet reductions.

12 Hypersensitivity events occurred in patients
13 without FCS in 2 cases. 2 cases occurred during
14 the development program. One was a report of serum
15 sickness in study CS16. Antidrug and anti-DNA
16 antibodies were positive in this patient and the
17 patient was treated with steroids and symptoms
18 resolve rapidly.

19 The second patient experienced a serious
20 adverse event of anaphylactic reaction. The
21 patient was treated with epinephrine and steroids
22 and the event resolved on the next day. And again,

1 antidrug antibodies were present 6 weeks prior to
2 this event.

3 Moving now to renal tolerability, there were
4 4 adverse events related to renal function in the
5 volanesorsen group, but none of these events were
6 serious, all of them resolved, and none resulted in
7 study discontinuation.

8 No patient in CS6 discontinued drug due to a
9 hepatic-related event and no patient treated with
10 volanesorsen met Hy's law. One placebo-treated
11 patient did in fact meet Hy's law criteria.

12 Now, adverse events related to hepatic
13 function occurred in both treatment groups without
14 a clear relationship to volanesorsen treatment.

15 In conclusion, the safety profile of
16 volanesorsen is well understood. The principal
17 safety concern is thrombocytopenia. Platelet
18 reductions occurred over several weeks and were
19 reversible. And there were no serious bleeding
20 events. With monitoring every other week and dose
21 reductions, platelet levels were managed and there
22 were no further dropouts in CS6. And we continued

1 to see improved patient retention in the open-label
2 study CS7.

3 From our experience in treating these
4 patients, we have developed a comprehensive risk
5 management program to further ensure safe use post-
6 approval. We remain committed to furthering our
7 knowledge of the safety profile of volanesorsen and
8 appropriately managing identified and potential
9 risks.

10 Thank you. Dr. Stevenson will now provide a
11 more detailed discussion of the risk management
12 program.

13 **Applicant Presentation - Michael Stevenson**

14 DR. STEVENSON: Thank you, Dr. Singleton.
15 Good morning. My name is Mike Stevenson and I'm
16 the vice president of global medical affairs at
17 Akcea Therapeutics. Let me now turn to our
18 comprehensive and integrated risk management
19 program.

20 Our risk management program focuses on
21 thrombocytopenia, which is the primary identified
22 risk of volanesorsen. We have consulted with FDA

1 on our proposed REMS program and have designed
2 measures to promote the safe use of volanesorsen in
3 patients with FCS.

4 As Dr. O'Dea mentioned, our comprehensive
5 risk management program consists of these 5
6 elements, labeling, REMS with elements to assure
7 safe use or ETASU, enhanced pharmacovigilance, a
8 patient support program, and a treatment registry
9 study.

10 Let me review these elements in greater
11 detail. Our labeling includes a modification to
12 our monitoring and dosing algorithm used in the
13 phase 3 clinical trial as well as other safety
14 elements.

15 These include weight-based dosing, a patient
16 medication guide, and early threshold for dose
17 pause. In this algorithm, all patients, platelets
18 are monitored at least every 2 weeks. Reductions
19 in platelet counts may trigger changes in either
20 dose regimen, monitoring frequency, or both, as
21 outlined in this table.

22 Patients with normal platelet levels who

1 weighed less than 70 kilograms will start with
2 weekly dosing for 3 months and then transition to
3 dosing every other week. Those who weigh more than
4 70 kilograms will dose weekly. If platelets drop
5 below 100,000, volanesorsen dose frequency changes
6 to every other week and platelet monitoring is
7 increased.

8 Declines below 75,000. Trigger a dose pause
9 and twice weekly platelet monitoring, whereas
10 values below 50,000 trigger expedited lab
11 turnaround time, rather, to enable daily platelet
12 monitoring with dose pause until platelet count
13 increases above 100,000.

14 If platelets fall below 25,000, we recommend
15 discontinuation of volanesorsen. The REMS and the
16 patient support program are designed to support the
17 adherence of this algorithm post-approval.
18 Furthermore, we will implement elements to assure
19 safe use as part of the REMS.

20 In collaboration with FDA, we based our
21 proposed REMS on an existing program. All patients
22 diagnosed with FCS, physicians, and especially

1 pharmacy must enroll in our program. No
2 volanesorsen will be administered if any of these
3 elements is absent.

4 First, before they can prescribe or dispense
5 volanesorsen, all physicians and the specialty
6 pharmacy will be certified. This will involve
7 training on the risk of thrombocytopenia, platelet
8 monitoring requirements, and adjusting the
9 volanesorsen regimen in accordance with the
10 algorithm.

11 Knowledge of these topics will be assessed
12 through a certification examination. Before
13 starting treatment, prescribers will counsel
14 patients on the benefit-risk profile, including how
15 to recognize signs of abnormal bleeding.

16 All volanesorsen-treated patients will be
17 registered to allow complete and close follow-
18 through of the requirements of the REMS program.
19 Finally, during treatment, prescribers will
20 document the safety of each patient by submitted
21 patient status forms every 90 days in order to
22 continue therapy. Pharmacies will have to verify

1 prescriber certification and patient authorization.

2 Dispensing will be limited to a 1-month
3 supply. An additional component of the risk
4 management program is enhanced pharmacovigilance.
5 This program is intended to provide early detection
6 of thrombocytopenia and to identify any trends in
7 platelet counts.

8 We will actively follow up on reported cases
9 with targeted adverse event questionnaires and
10 periodic aggregated safety reports will be
11 submitted to FDA. The pharmacovigilance system
12 will also monitor events, including injection site
13 reactions hypersensitivity, hepatic, and renal-
14 related safety.

15 A key component of the risk management
16 program is the patient support program or the PSP.
17 The PSP supports patient by facilitating compliance
18 with the monitoring. The cornerstone of this
19 program is a dedicated team of nurse case managers
20 who will focus on individualized patient services.

21 These will include scheduling blood draws
22 either at labs or through mobile phlebotomy, which

1 enables blood draws at home, work, or other venues
2 convenient for the patient with FCS.

3 In addition, the nurse case managers will
4 provide supplemental patient education, compliance,
5 and adherence tools. Further, the PSP will employ
6 a multifaceted alert system for healthcare
7 practitioners, specialty pharmacy, and patients
8 based on pre-specified platelet thresholds per
9 product labeling.

10 Let me walk you through some of the aspects
11 of the prescription generation as well as these
12 alert systems to demonstrate some of the program's
13 safeguards. Prescribers in the specialty pharmacy
14 must be certified prior to either the authorized
15 writing or dispensing of a volanesorsen
16 prescription.

17 If the prescriber does not attest to the
18 diagnosis of FCS or to patients being at least 18
19 years of age, no drug is shipped. Likewise, if the
20 prescriber or pharmacy isn't certified, no drug is
21 shipped. If a patient is diagnosed with FCS, they
22 will be registered into the REMS program. Failure

1 to register, no drug is shipped.

2 The patient receives their blood draw either
3 at a lab or with mobile phlebotomy. If a patient
4 misses a subsequent blood draw, the prescriber will
5 be contacted before drug is dispensed. The results
6 are sent to the prescriber, specialty pharmacy,
7 patient, and nurse case manager and analyzed. And
8 a specialty pharmacy verifies each order.

9 If the platelet count is normal, a 1-month
10 supply of volanesorsen is shipped to the patient.
11 Upon administration, the monitoring continues per
12 the dosing algorithm. If the patient count falls
13 below a threshold value, the prescriber, pharmacy,
14 case manager, and patient receive alerts from the
15 lab. The dose and monitoring will then be adjusted
16 according to the proposed algorithm.

17 An additional element, finally, beyond the
18 REMS program will be a post-commercialization
19 global registry study to follow more than 100
20 patients.

21 This study will assess trends, signals, and
22 potential adverse events, most notably

1 thrombocytopenia, and further characterize the
2 monitoring and dosing algorithm. This registry
3 study will also aim to characterize the
4 longitudinal safety of volanesorsen as well as
5 longitudinal effects on triglycerides and
6 pancreatitis.

7 In summary, we have proposed multiple
8 activities with checkpoints to manage patient
9 safety while making platelet monitoring and
10 compliance as straightforward as possible. Given
11 the high unmet medical need of patients with FCS
12 and the urgency to provide a specific treatment,
13 the proposed comprehensive and integrated risk
14 management program will support a favorable
15 benefit-risk profile post-approval.

16 Thank you, and Dr. Baum will now conclude
17 the presentation with his clinical perspective.

18 **Applicant Presentation - Seth Baum**

19 DR. BAUM: Thank you. I am Seth Baum,
20 current president of the American Society for
21 Preventive Cardiology, affiliate clinical professor
22 at the Schmidt College of Medicine and a practicing

1 clinical lipidologist and preventive cardiologist.

2 Today, we have seen compelling data from the
3 sponsors and other experts. We have heard that
4 familial chylomicronemia syndrome is an ultra rare
5 disease, conferring a 70 to 80 percent lifetime
6 pancreatitis risk. We know that the higher the
7 triglycerides, the greater the risk of severe
8 pancreatitis.

9 With each pancreatitis episode, patients
10 with FCS have a 6 percent risk of dying. The
11 clinical trial data prove that volanesorsen can
12 significantly lower triglycerides in patients with
13 no therapeutic options. No triglyceride-lowering
14 medicine is effective or approved in FCS, leaving
15 us, the treating physicians and the patients, with
16 no solutions.

17 The data also identify the thrombocytopenia
18 risk. In response to this, the sponsor has created
19 a comprehensive risk management strategy, including
20 the prescribing doctor, a specially trained nurse,
21 a single central laboratory, a single dispensing
22 specialty pharmacy, and the patient.

1 Additionally, the REMS was developed in
2 collaboration with FDA. The aim is to reduce the
3 risk of severe thrombocytopenia. In my view, the
4 sponsor has created a practical program for the
5 clinical setting. In fact, I have already seen
6 this work when treating my own patients. We
7 readily adhere to the algorithm.

8 The program has even included a robust
9 registry. It will inform us about this ultra rare
10 disease and help keep patients safe while affording
11 them the opportunity to receive this beneficial
12 drug.

13 Currently, I have one patient with FCS on
14 drug in CS7 and 3 patients with FCS eagerly
15 awaiting entry into the volanesorsen early access
16 program. Eagerly is an understatement. They are
17 literally begging to get in.

18 A 59-year-old woman with multiple
19 hospitalizations and procedures for pancreatitis, a
20 60-year-old man with diabetes as a consequence of
21 such severe pancreatitis, and a 47-year-old woman
22 with a persistent triglyceride level between 10,000

1 and 12,000.

2 All fully understand the risks of
3 volanesorsen, yet can't wait to be started on the
4 medication. That is because they know and live the
5 risk of not being on volanesorsen. They understand
6 that each episode of pancreatitis can be fatal.

7 This is not hyperbole. I am not
8 exaggerating. In fact, I am probably understating
9 their anguish and risk. They live in constant fear
10 of the next inevitable pancreatitis attack and its
11 associated risk of death. Volanesorsen is their
12 only option.

13 When I practiced interventional cardiology,
14 I'd constantly assess the risk-benefit
15 relationships of some of the most serious
16 interventions. With that experience in mind, now
17 as a lipidologist and preventive cardiologist who
18 treats patients with FCS, I am confident that
19 volanesorsen should be approved.

20 We have seen the data. We know the risks
21 and the benefits. We know that we need to monitor
22 the risks and we have the support system to do so.

1 Most importantly, this small group of patients
2 needs a therapy to lower their triglycerides.

3 Now, we can give them that opportunity by
4 recommending approval to the FDA. Thank you.
5 Dr. O'Dea will now return to take your questions.

6 **Clarifying Questions to Applicant**

7 DR. WILSON: Thank you very much. So the
8 next step that was just referred to is clarifying
9 questions for Akcea. Please remember, for those
10 posing questions, to state your name for the record
11 before you speak and please direct your questions
12 to a specific presenter.

13 And then once you're finished with your
14 microphone, push the red light off, so Dr. O'Dea,
15 yes, go ahead. Do we have a question? Dr. Burman,
16 go ahead.

17 DR. BURMAN: Thank you. Thank you for that
18 nice presentation. My question, though, for
19 clarification a little bit is for Dr. Singleton.
20 And my question is, if I quoted him correctly, he
21 said the safety profile of the agent is well
22 understood.

1 But I'd like his further comments on, number
2 one, the mechanism by which he thinks are as proven
3 that the platelet count is low, whether there's any
4 effective on vascular endothelium from this agent,
5 and I didn't see any results on platelet function,
6 just platelet numbers.

7 It appeared that some of the platelet
8 decreases were idiosyncratic in nature and couldn't
9 be predicted. Thank you.

10 DR. O'DEA: So Dr. Burman, if you wouldn't
11 mind, I'll ask Dr. Scott Henry to take that. He's
12 done a lot of our primary research to understand
13 this question. Dr. Henry is head of non-clinical
14 development at Ionis.

15 DR. HENRY: Yes, is this on? Scott Henry,
16 non-clinical at Ionis Pharmaceuticals. So we've
17 done quite a bit to study the effect on platelet
18 function specifically, including actually -- and a
19 lot of this has happened in our animal models,
20 where we can dig into this a little bit more.

21 So we've actually treated monkeys for a
22 period of time, 3 months, tested their platelet

1 function by traditional platelet aggregometry or
2 PFA-100, which is basically a coagulation test and
3 seeing no effect on platelet function.

4 Also in vitro we see no direct platelet
5 activation either in monkey or human platelets and
6 using related compounds, no impairment of the
7 platelet response to ADP or collagen normal
8 stimulants, also no increase in bleeding time.

9 To your question about other mechanisms,
10 essentially we've ruled out an effect on either
11 bone marrow production or other sort of
12 microangiopathy, thrombosis endpoints, and that
13 includes essentially excluding an effect on
14 endothelium.

15 We see no change in Von Willebrand factor.
16 So again, we've excluded a number of very important
17 mechanisms. Either make a karyocyte number or
18 function and thrombosis or endothelial
19 interactions. So that's the status of our
20 investigation at this point.

21 DR. WILSON: Dr. Newman?

22 DR. NEWMAN: My name is Dr. Connie Newman.

1 I'm from NYU and I have a question about the
2 baseline levels of triglycerides in the patients in
3 CS6. I understand that these patients were on
4 diet, but I was still very surprised to see there
5 were levels in the 300s.

6 Usually, patients with familial
7 chylomicronemia syndrome have triglyceride levels
8 of 2,000 or above as well as clinical symptoms. So
9 do you have any data on the triglyceride levels in
10 these patients before they were treated with diet?

11 DR. O'DEA: So if I could clarify, the
12 baseline triglyceride levels were 2,200 on average
13 in the patients after their 6 weeks of diet
14 introduction. Our patients, I think we mentioned,
15 were diagnosed in general in their 20s on average.
16 At the time they came to the study, they were in
17 their 40s.

18 DR. NEWMAN: I'm looking at CO-44, where the
19 circles show the baseline levels in individual
20 patients, so I'm just talking about individual
21 patients.

22 DR. O'DEA: So the blue circles are the

1 baseline at entry.

2 DR. NEWMAN: Right.

3 DR. O'DEA: The black squares are the final
4 3-month data. Right.

5 DR. NEWMAN: Right. And some of the blue
6 circles are very low.

7 DR. O'DEA: Yes. There are two circles,
8 which are below 750. Now, at the time the patients
9 were screened, all of the patients were at 750.
10 Some of the patients subsequently had slightly
11 lower values as they entered the study. But the
12 mean for the population was 2,200.

13 DR. NEWMAN: I have a question for
14 Dr. Rader. In your experience, what level of
15 triglycerides do patients with familial
16 chylomicronemia syndrome have? Because the
17 literature says 2,000 and above.

18 DR. RADER: Patients with FCS have
19 chylomicronemia, which generally starts to appear
20 over about 750 milligrams per deciliter. Certainly
21 many of these patients have even much higher levels
22 of triglycerides. It's absolutely true.

1 These patients in this trial were placed on
2 a very low fat diet, which adherence to is
3 relatively variable. And there's also variability
4 among FCS patients in terms of their response to
5 diet.

6 So I would suggest one possibility would be
7 those few individuals who had appropriate
8 triglycerides to get into the study, but then were
9 placed on the very low fat diet were adherent and
10 happened to have at least enough of a response to
11 bring their baseline triglycerides down to the
12 levels that we saw in that slide.

13 DR. NEWMAN: Thank you. Thank you.

14 DR. WILSON: Dr. Morrato?

15 DR. MORRATO: Thank you. Dr. Morrato. My
16 question is for Dr. Stevenson and the risk
17 management program. And I'm just trying to
18 understand a little bit, two points. One is the
19 scientific evidence in support of the monitoring
20 and evidence in terms of burden to the healthcare
21 system. So are you able to answer?

22 So my question is, we have a lot of examples

1 in medicine in which you have rare adverse events
2 that we say, let's go ahead and monitor them on a
3 certain frequency.

4 DR. O'DEA: Right.

5 DR. MORRATO: It sounds good on paper, but
6 there's really little evidence that would say that,
7 that excess monitoring is going to have a return on
8 that investment so to speak. So if you look at
9 slide CO-78, where you have your proposed weight
10 and monitoring recommendation, what is the
11 scientific evidence in support of this
12 recommendation?

13 DR. O'DEA: So of course, our evidence is
14 empirical. We did not --

15 DR. MORRATO: Based on 33 patients? So tell
16 me, I couldn't find a good description in the
17 briefing documents, exactly how you -- is this a
18 model, algorithm? Please explain.

19 DR. O'DEA: So when we started our phase 3
20 program, we had a dose pause as a safety option
21 should we see any renal, hepatic, or platelet
22 changes. As we went forward in the program, as

1 Dr. Singleton noted, we saw two patients with an
2 acute severe thrombocytopenia.

3 Caused us to make a number of changes. One
4 of those changes was to change to allow a dose
5 adjustment option, meaning reduced dose. So as we
6 designed the trial with a small trial like that,
7 multiple doses will be a challenge to find
8 meaningful information on one versus the other. So
9 adding a dose adjustment was considered to be a
10 reasonable preventive step to come to, how shall I
11 say, mitigate this risk.

12 The second thing we did is, we changed the
13 range at which dose pauses happened. So
14 previously, dose pauses happened at a higher range.
15 We brought that up to about 75,000. So we put in
16 two mitigations.

17 Now, subsequently, in that trial, we had no
18 further platelet-associated discontinuations and
19 subsequently had no other of course severe
20 thrombocytopenia. So in our view, when people
21 adhere to this, we find that we're able to limit
22 the risk for patients.

1 When we completed the trial, one of the
2 important findings we had was that, looking to try
3 and understand both mechanistically as Dr. Henry
4 spoke about, but also with the demographics of the
5 treated population, could we identify demographic
6 elements that would help us.

7 So we looked from a pharmacologic
8 perspective. We looked at the rapidity of an early
9 platelet production, like 20 percent, 30 percent,
10 40 percent, 50 percent in the first month at
11 3 months as regards whether that would be a signal
12 that we could harness to ensure the safety of
13 subjects.

14 We also looked at relationships between
15 basal triglycerides and the risk of
16 thrombocytopenia. We do know that the FCS
17 proportion has a background risk of
18 thrombocytopenia independent of any therapy. They
19 haven't published and described.

20 They are a high-risk population. They may
21 run a higher risk than other populations. We did
22 not see the same level of thrombocytopenia in other

1 populations that we've studied.

2 So one of the insights that we had was
3 looking at the data both in CS6, which is the FCS
4 population, and CS16, which is non-FCS
5 hypertriglyceridemic population, is that there is a
6 correlation between the maximum reduction in
7 platelets and the overall body weight.

8 The slope of the line in both of those
9 studies are consistent, one with the other. So we
10 do think the body weight related to exposure is an
11 important factor in this.

12 DR. MORRATO: So what's the evidence of the
13 threshold of 70 kilograms?

14 DR. O'DEA: So the evidence for 70
15 kilograms, I think, is WT-4 slide if you don't
16 mind. So I just put up this slide. And again,
17 this is after we've concluded the trial, just to be
18 absolutely sure.

19 So when we look at patients who are less
20 than 70 kilos versus patients who are greater than
21 70 kilos, first thing one notices is that there's a
22 difference in exposure. The second thing one

1 notices is that the reduction in platelets in the
2 second yellow highlight is 63 percent, 62 percent,
3 versus 43 percent in the heavier patients, while at
4 the same time, looking at triglyceride response,
5 was still seeing a very substantial triglyceride
6 response of 60 percent versus 72 percent.

7 DR. MORRATO: So if I'm reading that
8 correctly, that's 11 and 8 patients?

9 DR. O'DEA: That's correct.

10 DR. MORRATO: So assuming it's practical, is
11 this being employed in the open label?

12 DR. O'DEA: So the open-label trial had
13 completed enrollment and so it is not -- and so our
14 label as you may have seen is, first 3 months, the
15 patients are on 300 milligrams. On a weight basis,
16 they automatically go to a lower dose.

17 So all patients have passed that point when
18 we made this determination. We are looking at our
19 early access program and it is implemented in our
20 early access program.

21 DR. MORRATO: Can I ask one question? So
22 the open label is evidence of someone being able to

1 sustain these recommendations over a long period of
2 time. When I look at one of the slides that you
3 presented, it looks like only 27 percent of
4 patients are actually sustaining with this
5 monitoring.

6 I know that your program was done in 20
7 countries. How much of that is really evidence
8 that this is workable in the United States
9 healthcare system?

10 DR. O'DEA: So if I could clarify one point,
11 it's that we do have an 80 percent retention of
12 patients on the open-label extension study. We had
13 a 60 percent, you're correct, before we instituted
14 this change.

15 So we do have indirect evidence that it
16 shows some benefit having patients on this more
17 flexible dosing regimen and also monitoring
18 regimen. In terms of our assessment of our impact
19 on the healthcare system, I'm not sure that we have
20 the right people to answer that question, but
21 perhaps from our deeper team, we can come back to
22 you after the break.

1 DR. WILSON: Thank you. I'm sure we're
2 going to come back to dosing and other discussions.
3 So Dr. Neaton is next.

4 DR. NEATON: I have a question. It's really
5 clarification. It might be helpful to pull up
6 slide 47. So you mentioned, which I was glad to
7 hear, that you made every attempt to get people
8 back for triglyceride and other measurements
9 following treatment discontinuation, as I
10 understood it.

11 But if I look at this slide and the numbers
12 below, am I interpreting it correctly that, of the
13 14 people who discontinued, only about half of them
14 returned for visits for triglyceride measurement?

15 DR. O'DEA: So all but 6 patients continued
16 to return for continued assessment of
17 triglycerides.

18 DR. NEATON: So the numbers here, these
19 weeks; does this correspond to what you referred to
20 as your standard visit schedule?

21 DR. O'DEA: It does, but these are the on-
22 treatment patients. This is the observed data.

1 The on-treatment --

2 DR. NEATON: The non-completers, I am
3 assuming, are among the 14 that didn't complete the
4 study.

5 DR. O'DEA: The non-completers are, yes, the
6 14 that didn't complete the trial. They are not
7 represented in that data. They were represented in
8 the previous slide, which is a full analysis set.

9 DR. NEATON: I guess I'm not understanding,
10 then, because these numbers -- maybe you just need
11 to clarify what these numbers are, then.

12 DR. O'DEA: Sorry. I should clarify. So as
13 you can see, among the dose non-reduce -- perhaps
14 the semantics are poor -- there are 6 patients who
15 continued on 300 the whole way through, 12 patients
16 who continued with the dose reduction, and there
17 were 6 patients who did not reach the end of the
18 trial, as you can see, in that graphic, all
19 contributing to that dataset.

20 DR. NEATON: The legend at the top says the
21 gray line corresponds to 14 non-completers.

22 DR. O'DEA: That's right.

1 DR. NEATON: As I look at the numbers going
2 across, it's less than half of that at the end,
3 right around half of that. And so basically, the
4 people who discontinued treatment must not have
5 been coming back for triglyceride measurement. Is
6 that correct?

7 DR. O'DEA: So there are 6 patients who were
8 coming back for regular assessments.

9 DR. NEATON: That's kind of what my question
10 was.

11 DR. O'DEA: Yes.

12 DR. NEATON: So a related question
13 concerning follow-up, and we can come back to it
14 later; your diagnosis of pancreatitis began with a
15 review of a serious adverse event report. Correct?

16 DR. O'DEA: That's correct.

17 DR. NEATON: That has been adjudicated.

18 DR. O'DEA: That's right.

19 DR. NEATON: So what were the criteria for
20 reporting serious adverse events following
21 discontinuation of therapy?

22 DR. O'DEA: So all serious adverse events

1 were reviewed by the adjudication committee, not
2 serious adverse events alone that resulted in
3 discontinuation. So they had a constant feed of
4 serious adverse events.

5 DR. NEATON: But your protocol stipulated
6 that, even when a person stops blinded study
7 treatment, they were to report serious adverse
8 events?

9 DR. O'DEA: That's correct. That's correct,
10 at the milestone visits.

11 DR. NEATON: Did any pancreatitis events
12 occur after discontinuation of blinded treatment?

13 DR. O'DEA: No. The patient on volanesorsen
14 who had an event of pancreatitis had a triglyceride
15 value of 300 and previously most recent injection
16 was about 2 weeks previously.

17 DR. NEATON: We'll come back to this.

18 DR. WILSON: Dr. Everett?

19 DR. EVERETT: Thanks. I actually have two
20 questions, the first on that same slide that we
21 were just looking at. I guess it's 47. Is that
22 right?

1 DR. O'DEA: That's correct.

2 DR. EVERETT: So specifically, this is
3 perhaps informed by Dr. James's comments, where we
4 have a persistent effect and you yourself made that
5 point in your presentation. In those who did not
6 complete, there was a persistent effect of the
7 medication on triglycerides. And so part of me is
8 wondering why the dosing regimen is weekly if it
9 seems like, when you discontinued therapy, there's
10 a prolonged effect.

11 Given the effects on the risk, maybe you can
12 comment on why you selected a weekly dosing regimen
13 for this particular medication.

14 DR. O'DEA: So the weekly dosing regimen was
15 selected on the basis of the phase 2 trial, where
16 we treated subjects, 100, 200, and 300 milligrams.
17 And as mentioned, at that time, there was no
18 safety signal on platelets nor on any other
19 parameter, so the decision was made to go forward
20 with 300 weekly in view of the severity of the
21 disease and the grade of elevation of triglycerides
22 that this population exhibit.

1 So that was the basis of it. Subsequently,
2 to your point, yes, we did see those declines of
3 platelets, which occurred in general around 3 to
4 6 months to 9 months of exposure with drug at the
5 300-milligram range. And that's why we decided at
6 that point to make an adjustment to the dosing
7 paradigm to ensure that patients could enjoy the
8 benefits of treatment without having to discontinue
9 treatment.

10 If I could just comment on the data, there
11 is censoring of that data, as you can probably
12 estimate. There are 1 or 2 patients whose samples
13 weren't right on that date. They may have been a
14 week earlier or a week later, but it had to be
15 within 2 days of the assessed date.

16 DR. EVERETT: So given that you made a
17 decision after the randomized trial to adjust the
18 dosing regimen based on weight, you adjusted dose,
19 but not necessarily interval. Correct? And have
20 you tested either approach? Is the most effective
21 way to minimize the risk by reducing the dose or is
22 it by reducing the frequency and the dose or just

1 one or the other?

2 DR. O'DEA: So at the present time, our
3 approach to dose reduction has been frequency
4 reduction, just to make that clear. We've had a
5 single presentation of 300 milligrams weekly. The
6 patients did self-inject, by the way. I don't
7 think we made that clear.

8 We are preparing a 150 syringe at the
9 moment, recognizing what we found in our analyses
10 of these data, that there is a weight-based element
11 to the risks that the patients have. For the
12 present time, alternate-week therapy is
13 pharmacologically from the modeling perspective and
14 also from the actual data that we have a reasonable
15 and suitable approach to reducing dose. And again,
16 to your point, these are drugs which can be given
17 on a weekly, biweekly, monthly basis because of the
18 long half-life.

19 We want to make sure that, for us, the
20 preference is to move to more frequent, lower dose
21 in the end.

22 DR. EVERETT: But just to be clear, you've

1 not actually tested any of those strategies in
2 their efficacy on triglycerides or their risk on
3 thrombocytopenia and other adverse events.

4 DR. O'DEA: So we don't have any data at the
5 present time. We are collecting that data at the
6 present time.

7 DR. EVERETT: I'm sorry. And then my second
8 question really has to do with the diagnosis of FCS
9 because it seems to be fundamental. If you look, I
10 think it's slide 82. Yes. On your risk management
11 program, in the top left, we have adult patient
12 with confirmed diagnosis of FCS. I haven't seen
13 any proposed diagnostic criteria and I know that
14 there's some discrepancy and difference. We heard
15 a little bit from Dr. Rader about how one might
16 make the diagnosis.

17 Since this is fundamental to who gets the
18 drug and, from what I understand, given the unmet
19 medical need in a particular and focused population
20 where the risks which we've discussed might
21 actually be balanced by the benefits, we need to
22 know exactly who will be getting the drug.

1 So what's your proposal for the actual
2 confirmed diagnosis of FCS?

3 DR. O'DEA: So the population we studied
4 were populations characterized, number one, by
5 hypertriglyceridemia greater than 750, number two
6 by the presence of a major genetic marker for the
7 disease, and number three, by the presence, if in
8 the absence of a major genetic marker of a
9 positive, that is, a low response to the LPL assay,
10 so we use all of the --

11 DR. EVERETT: So you would propose a genetic
12 test and an LPL functional assay in every patient.

13 DR. O'DEA: That's right. Yes, that was
14 required for our trial.

15 DR. EVERETT: How accessible and available
16 are those in the United States and more broadly?

17 DR. O'DEA: So the LPL assay is not that
18 available. I'll ask Dr. Rader to talk more
19 generally, though, about the genetic testing.
20 Genetic testing, of course, we will facilitate, but
21 it requires to ensure that patients are
22 appropriately identified and can be treated

1 appropriately. Dr. Rader?

2 DR. RADER: Thank you. This is clearly a
3 very important issue, obviously, the identification
4 of the patients with FCS who are candidates for
5 this medicine. It's important to point out that,
6 currently, the diagnosis offices is a clinical
7 diagnosis. These are patients who generally refer
8 to lipid specialists who make the diagnosis based
9 on clinical criteria, which include persistently
10 elevated severe, severely elevated triglycerides
11 over 750, not just one measurement, but multiple
12 measurements.

13 The absence of secondary causes such as
14 insulin resistance, diabetes, alcohol use, which by
15 the way I think is an important distinguishing
16 characteristic because many of the non-FCS
17 patients, if not most of them who have severe
18 hypertriglyceridemia and chylomicronemia have other
19 secondary factors that contribute to that.

20 The third is the refractoriness to
21 medication, to response to medication. Both
22 fibrates and fish oils; at least part of their

1 mechanism requires good LPL activity. So I see
2 lack of responsiveness to those existing
3 medications as, if you will, almost a surrogate
4 sign for a lack of good LPL activity.

5 Then certainly a history of pancreatitis or
6 abdominal pain and certainly those who had some
7 sort of presentation in childhood with either
8 severe hypertriglyceridemia or pancreatitis is a
9 very important criterion, not required, but
10 certainly helps to mark a patient with FCS.

11 So that's the clinical diagnosis that we as
12 lipidologists use to make this diagnosis. It's
13 really only a tiny fraction of the broad number of
14 patients who have chylomicronemia.

15 LPL testing is very attractive conceptually,
16 but there is no clinically available assay right
17 now and, frankly, it's a challenging assay. So
18 we'd love to see that happen, but it's not
19 available now.

20 Genetic testing, of course, is attractive as
21 a geneticist. When you find the two mutations, you
22 feel like you've really confirmed the diagnosis. I

1 think the problems with mandating genetic testing,
2 although I think this is a discussion that needs to
3 continue to be had, is, one, it's not currently
4 being done clinically. It's not part of the
5 clinical approach to this disease currently in the
6 U.S.

7 Second, there are issues with how we would
8 actually pay for those genetic testing. It's not
9 standard right now for even insurance to pay for
10 genetic testing. Hopefully that could be changed.
11 And then third, it is important to point out that
12 lack of finding two mutations in my view does not
13 rule out the diagnosis.

14 There are other genes that are involved.
15 Next-gen sequencing can miss certain types of
16 things like large deletions. And so I do think the
17 clinical diagnosis can be made even with a negative
18 genetic test.

19 DR. O'DEA: So it sounds like you would not
20 advocate using an LPL functional assay or a genetic
21 test to identify patients who would be potentially
22 candidates for using this medication.

1 DR. RADER: LPL testing is really
2 attractive, but I can't advocate it in the absence
3 of a robust, reliable test that could be used
4 diagnostically. Genetic testing, I think, is
5 appealing for clinicians who want to augment their
6 clinical experience and diagnosis with a genetic
7 test.

8 But I would hate to see patients who really
9 do have FCS based on clinical criteria be denied
10 this medication simply because we're unable to find
11 a specific genetic mutation in the 5 genes that are
12 currently being tested.

13 DR. O'DEA: Yes. I think there's that
14 problem, but there's the opposite problem, too,
15 which is that somebody who has an alternative cause
16 for hypertriglyceridemia is exposed to a medication
17 that may not have benefit for them, but has
18 substantial risks.

19 DR. RADER: I certainly understand that
20 concern.

21 DR. WILSON: Let's go on to the next.
22 Dr. Low Wang?

1 DR. LOW WANG: Thank you. I have two
2 questions. The first is what proof you have that
3 the increased platelet monitoring works. So one of
4 my concerns is that the thrombocytopenia seems to
5 be idiosyncratic in certain instances.

6 Since the increased monitoring program was
7 instituted, there have been at least 1, possibly 2
8 cases of severe thrombocytopenia that have
9 occurred.

10 DR. O'DEA: So Dr. Stevenson spoke to the
11 fact that one of the learnings from this is that an
12 algorithm is as good as the adherence to it. And
13 it's very important on our part to ensure that we
14 have high adherence to the algorithm.

15 Part of the reason that we're building such
16 a degree of support behind it is to make sure that
17 everybody does adhere to it. In the instances
18 where we've had patients not follow the algorithm,
19 there has been human error. And obviously, human
20 error is something that is a struggle to prevent.

21 So the patient support services, having
22 multiple lines of communication, such that the lab

1 test for the patient is available through the
2 central lab, it's available of course to the
3 prescribing physician. It's available to the nurse
4 case manager and through an app which is being
5 developed or has been developed, is available to
6 the patients.

7 So the physician will be informed by a nurse
8 case manager that there is a result which is
9 flagged to ensure that that's not missed. The lab
10 will call the physician office to ensure that the
11 physician is aware also, so we have two lines
12 directly in to the physician office in case
13 somebody failed to notice the lab result which came
14 to the office.

15 So we're putting in place a number of these
16 elements to triangulate around the possibility that
17 somebody may not know. There's also a patient
18 guide. There's patient education programs built
19 into the program to ensure that the individual
20 patient is fully aware of the need and for
21 adherence and the risks of non-adherence.

22 DR. LOW WANG: I think that my concern is

1 that it could be idiosyncratic, so increased
2 monitoring would not necessarily make a difference.
3 So that's one question. My second question is for
4 Dr. Stevenson and this has to do with an element of
5 the REMS program and just the definition or the
6 rationale.

7 This is on slide 78. So in terms of
8 platelet monitoring, going back to that point, what
9 stable means and what the rationale is for that?

10 DR. O'DEA: So to your point about
11 idiosyncratic, yes, they're the cases that we have
12 listed and they're the cases that we discussed in
13 detail to ensure that the gradual decline is
14 predictable. It's the occasional patient who has
15 this idiosyncratic response, who is the focus of
16 all of this program.

17 DR. STEVENSON: Mike Stevenson, head of
18 global medical affairs. The question and the
19 definition as I understand it is what is the
20 definition of stability. The way that we have
21 defined it and why it was written that way in the
22 table is that we often leave to the discretion of

1 the physician on multiple readings to show some
2 consistency across those multiple readings at
3 levels above 100,000, which is a recognized value,
4 above which the risk of serious bleeding is
5 considerably mitigated.

6 DR. LOW WANG: I think, in this case,
7 though, the word stable is used for patients with
8 platelet counts that are below 75,000.

9 DR. STEVENSON: Correct. And the
10 recommendations for the dose regimen is pause and
11 resume every other week when platelets are above
12 100,000. So the implication -- and apologies if
13 it's not clear on this -- is that the levels will
14 go above 100,000 on multiple readings until you see
15 consistency of that level being at least 100,000 or
16 above.

17 DR. LOW WANG: Thank you.

18 DR. STEVENSON: Thank you.

19 DR. WILSON: Thank you. Dr. Shamburek?

20 DR. SHAMBUREK: Thank you. Diet therapy is
21 very key to the long-term success in the familial
22 chylomicronemia syndrome. And we've seen several

1 times the one slide where the placebo increases
2 somewhere, 19 percent. And I have two questions,
3 but the first is, do you have any follow-up on
4 dietary compliance at the 6 or 12 months?

5 It seems to me that increase is likely, that
6 that 6- or 8-week period of screening with diet was
7 no longer followed and that would represent it.
8 That would be one. My second question gets around
9 probably the safety issue with your REMS proposed
10 program. And I suspect we'll hear more about it.

11 But will that limit the prescriber to the
12 inclusion criteria that you've suggested here? In
13 my practice, it's often the children that are at
14 the highest risk that may not make it to adulthood,
15 that by the time they make it to adulthood, they
16 have chronic pancreatitis.

17 So would a REMS program preclude off-label
18 use and only define to that? And what is your
19 likelihood of a patient with this getting a blood
20 draw done 26 times a year for presumably lifelong
21 therapy?

22 DR. O'DEA: So I count five questions there.

1 The first is the issue of diet. During the course
2 of our trials, we did ensure that patients were
3 instructed at every visit about diet. We did have
4 recall on diet.

5 What we did not do is a random recall survey
6 of the patients within the trial. Part of the
7 reason is, of course, it's subjective and it's up
8 to the patient to provide that information.

9 All of our patients are well-curated
10 patients. I mentioned their age of diagnosis.
11 They're 20 plus years into their disease. They're
12 all at the leading centers in the world like
13 Dr. Rader's center or Dr. Baum's center. And they
14 are fully aware of the risk of deviating from the
15 diet.

16 As regards to the REMS, it's our intent that
17 the entry to the REMS, of course, is based on
18 adherence to label, i.e. only those who meet the
19 criteria for the product label, only those who are
20 informed of the risks and benefits provided in the
21 product label will be those who are treated.

22 As regards to younger patients, as

1 Dr. Stevenson said, our intent is that this is a
2 drug for adult patients. We have not yet studied,
3 although we have filed, a pediatric protocol to
4 continue the development with a significant change
5 in our dosing paradigm for pediatric patients for
6 initiation in the very near future.

7 We also have a PIP, so called in Europe, for
8 the continuation of development in that age group.
9 And you're correct; the pediatric population are at
10 risk. We do need to accelerate our access to the
11 drug in that population, but at the present time,
12 we have not reached the point where we have a
13 submissible filed for the pediatric population.

14 DR. WILSON: Excuse me. Dr. Budnitz?

15 DR. BUDNITZ: Dan Budnitz. I have a
16 clarifying question on slide CO-66, I think that
17 Dr. Singleton was presenting. This is a figure of
18 platelet count by study week. And as in the
19 placebo group and volanesorsen group, N is 33 in
20 each. How were dropouts indicated in this figure?
21 As folks dropped out or discontinued from low
22 platelets or any other reason, how are subsequent

1 platelet counts counted and included in these lines
2 or are they excluded? So in other words, at the
3 end of the study period, the N would not be 33 in
4 this group. It would be much lower.

5 DR. O'DEA: So perhaps I'll take that
6 question for Dr. Singleton. We believe that these
7 are all available data in the population; i.e., the
8 patients who are continuing in their milestone
9 visits who may no longer be on drug.

10 So to your point, this represents a
11 combination of the completers, the non-completers,
12 and the dose-adjusted population.

13 DR. BUDNITZ: So in other words, people who
14 continued the medication, but still get subsequent
15 platelet counts are still considered on treatment?

16 DR. O'DEA: They are still considered in
17 study.

18 DR. BUDNITZ: In study.

19 DR. O'DEA: In study, yes.

20 DR. WILSON: We're going to stop now and
21 take a break. Some of the advisory committee
22 members have questions and we'll come back to that.

1 We have a list of their names. So let's see. You
2 had another reminder from me about lunch. Do you
3 have that to pull it up? The advisory committee
4 needs to choose their lunch and have their credit
5 card with them to pay for lunch. And they can do
6 that at the break and we'll direct you. And we'll
7 be back in 15 minutes. Okay?

8 (Whereupon, at 10:04 a.m., a recess was
9 taken.)

10 DR. WILSON: We are going to start in about
11 a minute. We're going to get going and what's
12 going to happen is, next, we're going to have the
13 FDA make a presentation.

14 Then we're going to come back to the more
15 than a handful of advisory committee questions to
16 the sponsor, because if we want any additional
17 estimates for things for this afternoon, it gives
18 them more time rather than coming back after lunch.

19 So next is FDA, then sponsor clarifying
20 questions, then FDA clarify. Okay? So I have to
21 find the right page. An FDA presentation; is that
22 going to be -- Dr. Roberts is already up there. I

1 was looking in the wrong direction, Dr. Roberts.

2 Thank you.

3 **FDA Presentation - Mary Roberts**

4 DR. ROBERTS: Good morning, members of the
5 committee. My name is Mary Roberts and I am the
6 clinical reviewer for the volanesorsen application.

7 This is the outline of the topics we
8 addressed in this morning's FDA presentations,
9 which were previously discussed in Dr. Sharretts'
10 introductory remarks.

11 I will begin with an overview of familial
12 chylomicronemia syndrome and aspects of its
13 diagnosis. Familial chylomicronemia syndrome or
14 FCS is a rare autosomal recessive disease caused by
15 biallelic pathogenic mutations in genes for the
16 enzyme lipoprotein lipase or its cofactors, which
17 are listed in the table below and are necessary for
18 LPL function.

19 Pathogenic mutations result in absent or
20 severely reduced LPL enzymatic activity, leading to
21 inadequate processing and clearance of
22 triglycerides, primarily from chylomicrons,

1 resulting in persistently elevated triglycerides.

2 Total loss of function mutations in the LPL
3 gene are the most common mutations observed with
4 FCS. Very few families have been described in the
5 literature as having homozygous cofactor
6 mutations. The prevalence for FCS is quoted as 1
7 to 2 per 1 million individuals.

8 The classic presentation of FCS is
9 characterized by onset of symptoms in childhood or
10 adolescence. However, symptoms may occur earlier,
11 during infancy, and in some individuals symptoms
12 may occur later such as during pregnancy.

13 Individuals with FCS have persistent very
14 high levels of triglycerides, which increases their
15 risk of pancreatitis. Pancreatitis is the most
16 serious and potentially life-threatening
17 consequence of this condition.

18 However, not all patients with experience
19 pancreatitis despite very high triglyceride levels.
20 More frequent events reported by patients living
21 with FCS include episodic recurrent abdominal pain.
22 Clinical signs include erupted xanthomas, lipemia

1 retinalis, a milky appearance to retinal vessels
2 which does not typically impair vision, and
3 hepatosplenomegaly. Other reported symptoms
4 include fatigue, forgetfulness, and depression.

5 Currently, a restrictive low fat diet of
6 less than 20 grams of fat is the mainstay of
7 therapy and can be effective if adhered to.
8 Triglyceride-lowering drugs such as fibrates
9 typically do not reduce triglycerides in this
10 population. There are currently no FDA-approved
11 therapies for the treatment of FCS.

12 Given that there are serious safety concerns
13 related to volanesorsen treatment, the ability to
14 identify patients with FCS for whom benefit could
15 be expected to exceed risk is a critical
16 consideration.

17 The applicant, in their background
18 materials, has stated that a specific diagnosis of
19 FCS can be made by using the following clinical
20 criteria. A patient with fasting triglyceride
21 levels greater than 750 milligrams per deciliter
22 that a refractory to standard triglyceride-lowering

1 therapy and at least 1 of the following; a history
2 of pancreatitis as an adult or child, history of
3 recurrent abdominal pain without other explainable
4 cause, or family history of hypertriglyceridemia,
5 and exclusion of other risk factors associated with
6 elevated triglycerides such as poorly-treated
7 diabetes.

8 According to the applicant, genetic testing
9 is considered supplemental and not necessary to
10 make a diagnosis.

11 Since more than 1 million Americans may have
12 triglyceride levels greater than 750 milligrams per
13 deciliter and since a family history of
14 hypertriglyceridemia is likely quite common given
15 the prevalence of diabetes and obesity in the
16 United States, it seems unlikely that these
17 criteria can make the diagnosis of FCS with
18 specificity.

19 In contrast, a recent diagnostic algorithm
20 for FCS proposed genetic testing as a fundamental
21 step in establishing the diagnosis in patients
22 clinically suspected of having FCS.

1 Furthermore, a recently updated gene review
2 stated that the majority of individuals with
3 chylomicronemia and plasma triglyceride
4 concentration greater than 2,000 milligrams per
5 deciliter do not have familial LPL deficiency,
6 which is the most common cause of FCS.

7 This afternoon, the committee will be asked
8 whether the proposed treatment indication of
9 familial chylomicronemia syndrome without further
10 definition specifically identifies a patient
11 population for whom volanesorsen may have a
12 favorable benefit-risk profile.

13 I will now discuss the key interactions
14 between the division and the applicant that
15 resulted in the volanesorsen phase 3 program. At
16 the end of phase 2 meeting in 2014, major topics of
17 discussion included the patient population,
18 selection of endpoints, the adequacy of the safety
19 database, and the appropriateness of the dose,
20 which are summarized in this table.

21 Two topics discussed, clinical endpoints and
22 dose selection, call for further attention. The

1 primary endpoint of triglyceride reduction in adult
2 patients with FCS was considered acceptable.

3 However, given the uncertainty regarding direct
4 clinical benefit to patients when using a biomarker
5 to support approval, the Division strongly
6 recommended assessing other outcomes that would be
7 meaningful to patients living with FCS.

8 In the phase 3 trial, a patient-reported
9 outcome measurement for abdominal pain, quality of
10 life questionnaires, and adjudication of
11 pancreatitis events were incorporated to more fully
12 inform the meaningfulness of triglyceride lowering.

13 In addition, the Division encouraged the
14 applicant to study more dosing regimens than only
15 300 milligrams per week in the phase 3 program in
16 case this regimen proved less safe or tolerable
17 than anticipated. No further phase 2 dose
18 exploration trials were initiated and phase 3
19 trials utilized a single dose regimen of 300
20 milligrams per week.

21 Following these discussions, 2 randomized
22 placebo-controlled studies were initiated called

1 study CS6 and CS16. CS6 is considered the pivotal
2 study to support the efficacy and safety of
3 volanesorsen in patients with FCS. CS16 provides
4 supplemental safety data.

5 Due to serious events of thrombocytopenia,
6 the dosing interval for all patients in CS16 was
7 changed to every other week at week 13, with the
8 exception of patients that had received 5 months or
9 more of treatment.

10 CS7 is an ongoing open-label extension study
11 in patients with FCS. Next, the key inclusion
12 criteria will be highlighted. Patients enrolled in
13 study CS6 qualified for participation by having a
14 history of chylomicronemia, defined as lipemic
15 blood or triglycerides greater than 880 milligrams
16 per deciliter as well as a fasting triglyceride
17 greater than 750 milligrams per deciliter at
18 screening, documentation of a genetic profile
19 consistent with FCS or documentation of low LPL
20 activity, and most patients were required to have a
21 history of pancreatitis.

22 Patients enrolled in CS16 required a fasting

1 triglyceride of greater than 500 milligrams per
2 deciliter in order to participate. Eligibility
3 criteria related to FCS for the open-label
4 extension study were the same as the pivotal trial.

5 The baseline characteristics of CS6 and CS16
6 are shown in this slide. Within the respective
7 trials, baseline characteristics were well matched
8 between treatment groups and are not shown.

9 Compared with the trial population in CS16,
10 the patients with FCS in CS6 were slightly younger.
11 There was a lower proportion of men and BMI was
12 lower. As expected, baseline triglyceride values
13 and percentage of patients with a history of
14 pancreatitis were higher in the CS6 population.
15 Study CS16 had more patients with a history of type
16 II diabetes and concomitant use of statins compared
17 to patients in study CS6.

18 Recurrent abdominal pain is a characteristic
19 symptom that adversely affects the quality of life
20 of patients with FCS. Starting during the 6-
21 to 8-week diet run-in period through the end of the
22 study, patients completed a weekly disease symptom

1 diary.

2 Interestingly, during the screening period,
3 the majority of patients did not report having any
4 abdominal pain. Furthermore, of the patients
5 reporting pain at least once during this period,
6 only 6 patients in CS6 reported their worst weekly
7 maximum pain intensity as 7 or greater.

8 As mentioned earlier, patients enrolled in
9 study CS6 qualified on the basis of prior
10 documentation of an FCS-associated genotype or on
11 the basis of prior documentation of LPL deficiency
12 in association with other qualifying inclusion and
13 exclusion criteria.

14 Testing via next-generation sequencing of
15 hypertriglyceridemia-related genes was subsequently
16 performed on study in the reference laboratory for
17 patients who consented to such testing.

18 The applicant reported that 9 of 66 patients
19 who had screening triglycerides of 750 milligrams
20 per deciliter or higher did not have confirmatory
21 on-study testing consistent with FCS.

22 For 3 of these patients, the initial

1 assessment that their genotype was consistent with
2 FCS and qualified them for participation was not
3 confirmed by the on-study geneticist. Six of these
4 patients were enrolled based on low LPL activity by
5 medical history or initial on-study LPL activity
6 testing that was not subsequently confirmed by the
7 reference laboratory or not done.

8 These examples suggest that the diagnosis of
9 FCS may not be straightforward, since some patients
10 who investigators believed had FCS who had
11 triglycerides greater than 750 milligrams per
12 deciliter and even a history of pancreatitis did
13 not have a diagnosis confirmed with on-study
14 testing.

15 How best to identify a patient population
16 for whom volanesorsen may have a favorable benefit-
17 risk profile should be kept in mind while
18 considering the efficacy and safety profile of
19 volanesorsen.

20 The next part of the presentation will
21 consider the efficacy observed in volanesorsen
22 therapy in patients with FCS. The efficacy

1 evaluation relies on a single trial, CS6. The
2 primary endpoint was the change in triglycerides at
3 month 3.

4 Other endpoints of interest include
5 abdominal pain, quality of life, and pancreatitis.
6 The strengths of this trial include use of a
7 placebo control, the duration, the adjudication of
8 pancreatitis events, and the attempt to capture a
9 patient-reported outcome, abdominal pain.

10 Limitations of this trial include the lack
11 of additional systematic collection of other
12 outcomes that may be clinically meaningful to
13 patients living with FCS and the high rate of
14 discontinuation in the volanesorsen arm.

15 The statistical reviewer, Dr. Alex Cambon,
16 will discuss these topics further.

17 **FDA Presentation - Alexander Cambon**

18 DR. CAMBON: Good morning. My name is Alex
19 Cambon. I am the statistical reviewer of this
20 application and will be presenting the efficacy
21 results.

22 This is an outline of the topics I will

1 cover. I will give a brief overview of the primary
2 and secondary endpoints for study CS6. After
3 describe treatment discontinuation and missing
4 fasting triglyceride data or TG, I will discuss the
5 treatment effect for primary and secondary
6 endpoints as well as evaluations of select
7 exploratory and post hoc analyses.

8 I will then discuss issues with these
9 exploratory and post hoc analyses, including
10 difficulty in interpretation due to the large
11 number of these analyses. Then I will end with a
12 summary of the statistical issues and conclusions.

13 These are the primary and secondary
14 endpoints for study CS6. Note that these were the
15 only endpoints included in the hierarchical
16 multiple testing procedure to control type 1 error.
17 The primary efficacy endpoint was percent change
18 from baseline and fasting triglycerides at 3
19 months.

20 Secondary endpoints included percent change
21 in fasting triglycerides at 6 and 12 months,
22 proportion of patients achieving various

1 triglyceride cut points, change in hepatic volume,
2 and two outcomes incorporating abdominal pain
3 and/or pancreatitis that are of special interest
4 and will be discussed in detail later.

5 Now, I will describe the extent of treatment
6 discontinuation and missing triglyceride data on
7 the two treatment arms.

8 In this figure, the X axis represents weeks
9 from randomization, and the Y axis the proportion
10 of subjects were still on treatment over time. The
11 red line with long dashes represents the
12 volanesorsen arm and the black short dashed line is
13 for the placebo arm.

14 The graph demonstrates that patients on the
15 volanesorsen arm discontinued treatment at a much
16 higher rate than those on the placebo arm. By 6
17 months, 9 of 33 or 27 percent of subjects
18 discontinued volanesorsen while only 1 subject
19 discontinued placebo.

20 By 12 months, almost half had permanently
21 discontinued volanesorsen treatment. Note that,
22 here, we are describing permanent treatment

1 discontinuation. There were more patients who had
2 dose changes or interruptions on volanesorsen.

3 Now, I will show how treatment
4 discontinuation impacts missing data. This table
5 shows the relationship between treatment
6 discontinuation and missing triglyceride data.
7 Some, but not all patients who permanently
8 discontinued randomized treatment were followed up
9 for triglyceride assessments. Only 1 volanesorsen
10 patient had discontinued treatment and there were
11 no missing data on either arm at 3 months, the time
12 point of the primary endpoint assessment.

13 However, there were increasing amounts of
14 missing data over time impacting the assessment of
15 secondary endpoints. For example, 6 subjects or
16 18 percent of the volanesorsen arm were missing the
17 12-month triglyceride assessment compared to only
18 1 subject or 3 percent of the placebo arm.

19 All 6 subjects in the volanesorsen arm with
20 missing 12-month triglyceride data had also
21 discontinued treatment. This increasing treatment
22 discontinuation and missing data on volanesorsen

1 over time helps to understand triglyceride results
2 shown on the following slides.

3 Next, I present some key triglyceride
4 results. The analysis results demonstrated
5 superiority for the primary endpoint of percent
6 change in fasting triglycerides at 3 months using
7 the applicant's ANCOVA method.

8 On average, there was a 77 percent reduction
9 in triglycerides at 3 months on volanesorsen as
10 compared to an 18 percent increase on placebo.
11 This yielded a statistically significant absolute
12 difference in average percent change of
13 94 percentage points in favor of volanesorsen.

14 This figure compares the cumulative
15 distribution for percent change in triglycerides at
16 3 months for the volanesorsen and placebo groups.
17 The X axis represents the percent change in
18 triglycerides. Since decreases in triglycerides
19 are desired, better or lower values of percent
20 change are toward the left side of the graph.

21 The Y axis is the corresponding proportion
22 of patients in each group who had the degree of

1 percent change shown on the X axis or better.

2 There was a large separation between the cumulative
3 distribution functions for volanesorsen and placebo
4 groups.

5 For example, the vertical line at 40 percent
6 reduction in triglycerides shows that 88 percent of
7 patients on the volanesorsen arm had at least a
8 40 percent reduction compared to only 9 percent of
9 patients on the placebo arm.

10 At month 6, there was still a large and
11 significant treatment difference in percent change
12 in triglycerides, but the average effect in all
13 randomized patients was attenuated somewhat
14 compared to month 3. This is probably due to the
15 increased treatment discontinuation at month 6 on
16 the volanesorsen arm shown in a previous figure.

17 The applicant's method of imputing missing
18 data relies on a missing-at-random assumption and
19 treatment discontinuation is not taken into
20 account. Since missing data are strongly
21 associated with treatment discontinuation and any
22 effects of treatment are likely to go away after

1 treatment discontinuation, the missing-at-random
2 assumption is probably not accurate.

3 For this reason, I implemented a wash-out
4 imputation which assumes that the profile of
5 subjects with missing data is similar to the
6 profile of subjects on the placebo arm.

7 At month 12, there again was a large and
8 significant difference, although there was further
9 attenuation of the estimated treatment effect
10 relative to earlier time points, again probably due
11 to the increasing discontinuation over time on the
12 volanesorsen arm.

13 Analysis of the proportion of patients with
14 3-month and 12-month triglyceride assessments less
15 than select threshold values showed a similar
16 pattern. There was again a consistently large
17 separation between groups at 3 months for each
18 threshold.

19 However, the 12-month triglyceride threshold
20 analyses, while still all showing a statistically
21 significant difference between treatment groups,
22 had large attenuations in the separation compared

1 to 3 months.

2 For example, 82 percent of patients on
3 volanesorsen had a 3-month triglyceride assessment
4 below 1,000 milligrams per deciliter. However, at
5 12 months, there were only 42 percent of patients
6 on this arm who had an assessment below this
7 threshold value.

8 Now, I will present results for additional
9 select secondary endpoints. Here again are the
10 primary and secondary endpoints. Many of these are
11 triglyceride-related endpoints. Given that
12 triglyceride level is a biomarker, there was an
13 interest in secondary endpoints that directly
14 measure how patients function and feel.

15 In particular, I will now focus on the pre-
16 specified secondary endpoints, highlighted in red,
17 involving patient-reported abdominal pain and acute
18 pancreatitis.

19 The first of these involved the average
20 maximum intensity of patient-reported abdominal
21 pain over the treatment period. Each week,
22 patients completed a symptom diary in which they

1 were asked if they had abdominal pain in the last
2 week.

3 If they answered yes, they were asked to
4 report their maximum pain intensity during the
5 previous week on a 0 to 10 numerical rating scale
6 as shown in the figure on the slide. To obtain the
7 average maximum intensity for a patient, these
8 weekly maximum intensity observations were averaged
9 over all weeks during the treatment period.

10 The other planned secondary endpoint that
11 measured how patients function and feel was a
12 composite endpoint involving both abdominal pain
13 and acute pancreatitis. The number of composite
14 events, defined as either an abdominal pain score
15 of at least 4 during the on-treatment period, or an
16 adjudicated pancreatitis attack during the on-
17 treatment period, was calculated for each patient.

18 From this, a yearly rate or frequency was
19 derived for each patient. These frequencies were
20 then averaged over all patients at each treatment
21 group.

22 This figure shows the missing data pattern

1 over time for abdominal pain, including
2 intermediate missing data. The solid red line on
3 top is the proportion of missing data for
4 volanesorsen over time and the black dotted line is
5 for the placebo arm.

6 As with triglycerides, there was an
7 imbalance with a consistently higher missing data
8 rate on the volanesorsen arm during the treatment
9 period. Also, NOT shown, there were 7 patients on
10 the volanesorsen arm versus 1 on the placebo arm
11 that were not followed up for the entire 12-month
12 period for acute pancreatitis attacks.

13 Analyses of abdominal pain and acute
14 pancreatitis generally assumed missing data after
15 dropout were missing at random, a questionable
16 assumption given the greater dropout on
17 volanesorsen.

18 Furthermore, some analyses compared
19 treatment groups with respect to counts or
20 proportions of patients experiencing an event.
21 These analyses are particularly problematic and
22 likely biased toward volanesorsen.

1 Given the differences between treatment arms
2 in discontinuation, the placebo group would be
3 expected to show a greater frequency of events
4 simply due to the greater follow-up time, even if
5 volanesorsen had no effect.

6 Here are the results of these select
7 secondary endpoints that directly measure how
8 patients function and feel. Since the measurements
9 involve pain and acute pancreatitis, higher values
10 represent worse outcomes. We can see that not only
11 are these analyses not statistically significant,
12 but since the treatment difference is positive for
13 both endpoints, they also lack any favorable trend
14 toward the study drug.

15 For example, the on-treatment rate of either
16 a weekly abdominal pain score greater than 4 or an
17 acute pancreatitis attack was roughly 2.7 events
18 per year on volanesorsen, as compared to 2.0 on
19 placebo.

20 I also note that the hierarchical testing
21 procedure stops at the first of these two endpoints
22 since it is the first analysis in the hierarchy

1 that is not statistically significant.
2 Nevertheless, we also evaluated additional
3 exploratory analyses of direct measures of how
4 patients function and feel to explore whether there
5 were any supportive trends toward benefit.

6 In particular, we focused on additional
7 analyses of abdominal pain, pancreatitis, and
8 patient-reported outcome measures of quality of
9 life in the overall study population.

10 Here, I present results for the proportion
11 of patients who experienced any abdominal pain
12 during the treatment period as well as the worst
13 rather than the average weekly maximum intensity of
14 abdominal pain.

15 For these additional exploratory abdominal
16 pain endpoints, there is again no evidence of
17 benefit. Next, I present exploratory results for
18 pancreatitis attacks during the treatment period.

19 There were three patients with an attack on
20 placebo as compared to 1 with an attack on
21 volanesorsen. This difference was not
22 statistically significant. Furthermore, as noted

1 previously, a comparison of counts or proportions
2 is problematic due to the greater dropout on
3 volanesorsen, so a comparison of the yearly rates
4 for the on-treatment period plus 28 days averaged
5 over all patients is also shown here with a reduced
6 difference between the treatment groups.

7 While the previous slides show that there
8 was no evidence of effects of volanesorsen on
9 abdominal pain and pancreatitis in the overall
10 study population, it is important to point out the
11 limitations of these secondary and exploratory
12 analyses.

13 As Dr. Roberts mentioned earlier, there was
14 somewhat limited abdominal pain reported before and
15 during the study, with 74 percent of patients not
16 reporting any abdominal pain during the 6-week
17 screening period and 56 percent not reporting any
18 abdominal pain during the treatment period.

19 Furthermore, there were only 4 patients with
20 pancreatitis events during the treatment period.
21 This study was not enriched for patients with
22 recent abdominal pain and was likely not

1 statistically powered to detect effects on these
2 outcomes.

3 Therefore, while the study does not provide
4 evidence of effects on these outcomes, it also does
5 not rule out meaningful effects. I also evaluated
6 results for the patient-reported outcome measures
7 of quality of life. Here, I focus on the SF-36,
8 which includes 8 domains. I show month 3 and month
9 12 change from baseline analysis results for the
10 select SF-36 domains of physical functioning,
11 vitality, bodily pain, and physical role
12 functioning. For each domain, higher scores
13 represent a better health state than lower scores,
14 and the scores were on a 0 to 100 scale.

15 There were no consistently favorable trends
16 for these outcomes. Analyses of other SF-36
17 domains and of EQ-5D, another patient-reported
18 outcome measure of quality of life, also did not
19 show any consistent trends toward benefit.

20 Thus, in summary, planned secondary and
21 exploratory analyses of abdominal pain,
22 pancreatitis, and quality of life outcomes in the

1 overall study population did not show any evidence
2 of benefit.

3 However, the applicant has emphasized some
4 select subgroup analyses in its application
5 briefing document and in proposed labeling. In
6 particular, the applicant emphasized analyses in
7 the subgroup who had abdominal pain at baseline,
8 and in the subgroups who had at least 1, or at
9 least 2 pancreatitis attacks in the previous 5
10 years.

11 To interpret the results from these
12 analyses, it can be helpful to describe where these
13 analyses fit into the prospective plan and into the
14 range of analyses conducted by the applicant.

15 Here's an overview of the huge number of
16 endpoints and analyses that were planned and/or
17 conducted by the applicant. There were about 10
18 primary or secondary endpoints pre-specified in the
19 statistical analysis plan and included in the
20 hierarchical testing procedure.

21 In addition, there were over 100
22 exploratory/tertiary analyses pre-specified to

1 varying degrees in the analysis plan, but not
2 included in the multiple testing hierarchy.

3 This included those exploratory analyses of
4 abdominal pain, pancreatitis, and SF-36 in the
5 overall population that I just presented and that
6 did not show any evidence of drug effects.

7 Finally, there were greater than 100 post hoc
8 analyses, i.e., analysis that were not pre-
9 specified even as exploratory, but that I found in
10 the applicant's Study Report Body or report
11 synopsis.

12 The large number of exploratory and post hoc
13 analyses creates challenges for interpretation of
14 results. When there are so many endpoints and
15 analyses, low p values can easily occur by chance
16 alone even if there's no treatment effect. And
17 positive trends may reflect chance findings.

18 A few of these hundreds of analyses
19 emphasized by the applicant were unplanned analyses
20 of pancreatitis in the subgroup with a history of
21 pancreatitis.

22 In particular, here I show one such post hoc

1 subgroup analysis emphasized by the applicant. The
2 numbers of patients experiencing a pancreatitis
3 attack during the treatment period are shown here
4 for the subgroup of subjects with at least 1 prior
5 attack during the previous 5 years, and the
6 subgroup of subjects with at least 2 prior attacks.

7 The applicant has emphasized the observation
8 of 3 patients with events on placebo versus 0 on
9 volanesorsen and a nominal p value of 0.02 in a
10 subgroup with 2 or more attacks in the previous
11 5 years.

12 This subgroup analysis includes only 7
13 subjects on the volanesorsen arm and 4 on the
14 placebo arm. This is a very small subgroup taken
15 from an already very small population. Also, as
16 discussed previously, analyses involving counts do
17 not take into account the shorter follow-up time
18 for patients on the volanesorsen arm and therefore
19 bias results toward the study drug.

20 I also note that the complimentary subgroup
21 analysis on the bottom row, including only patients
22 with no prior acute pancreatitis attacks,

1 comprising almost two-thirds of the 66 randomized
2 subjects, showed 1 subject experiencing an acute
3 pancreatitis attack on the volanesorsen arm and
4 none on placebo.

5 Here, I summarize issues and conclusions
6 about the post hoc subgroup analyses emphasized by
7 the applicant. First, it is important to recall
8 that the secondary and exploratory analyses of
9 abdominal pain, pancreatitis, and quality of life
10 measures in the overall study population did not
11 provide any evidence of a treatment effect on
12 volanesorsen.

13 Furthermore, the analyses emphasized by the
14 applicant were selected from among hundreds of
15 analyses conducted, the vast majority of which did
16 not show such favorable trends.

17 Low p values are expected just by chance
18 with such a large number of analyses. Finally,
19 missing data likely bias results in favor of
20 volanesorsen, particularly for comparison of
21 counts, as in the pancreatitis analyses shown on
22 the previous slide.

1 Because of these issues, the results from
2 the subgroup analyses do not provide convincing
3 evidence of effects on supportive endpoints of
4 abdominal pain and pancreatitis.

5 Now, I'll summarize our key conclusions
6 about the efficacy of volanesorsen. Study CS6
7 demonstrated a large treatment effect on fasting
8 triglyceride level, both in terms of the mean
9 percent change and in terms of proportions of
10 patients meeting various threshold levels.

11 However, there was no evidence of benefit
12 with respect to abdominal pain, acute pancreatitis,
13 or quality of life measures. It should be noted
14 that CS6 was likely not optimally designed or
15 powered to detect differences in these endpoints
16 and that for rare outcomes such as acute
17 pancreatitis the number of events was likely too
18 small to reliably evaluate if volanesorsen has an
19 effect.

20 Therefore, while these analyses do not
21 provide evidence of effects, they also do not rule
22 out meaningful effects. Nevertheless, these

1 analyses lead to uncertainty about the magnitude of
2 effect on direct measures of how patients function
3 or feel.

4 Sources of information outside this trial
5 are thus needed to characterize the expected
6 magnitude of direct benefit for patients and to
7 weigh those benefits against the risks of
8 volanesorsen that will be discussed in upcoming FDA
9 presentations. This concludes my presentation. I
10 will return the podium to Dr. Roberts. Thank you.

11 **FDA Presentation - Mary Roberts**

12 DR. ROBERTS: The presentation on
13 volanesorsen safety will cover the following
14 topics. I will begin by discussing my approach to
15 the safety review and extent of patient exposure,
16 followed by an overview of adverse events, serious
17 adverse events, and discontinuations in both
18 placebo-controlled and open-label extension
19 studies.

20 Then I will describe the following safety
21 topics of interest; injection site reactions,
22 immunogenicity and hypersensitivity, renal and

1 hepatic events, and lastly the primary safety topic
2 of thrombocytopenia and risk of bleeding.

3 Individual review of the 3 phase 3 trials
4 was the main source of data to derive my
5 conclusions regarding the risks observed with
6 volanesorsen therapy. The primary focus of the
7 safety review was CS6, the 1-year placebo-
8 controlled trial in adult patients with FCS.

9 Supportive safety data was provided in CS16,
10 a 26-week placebo-controlled trial in patients with
11 high triglycerides. Since the primary purpose of
12 CS16 was to supplement the safety profile of
13 volanesorsen compared to placebo, my presentation
14 describes the comparison of all volanesorsen-
15 treated patients with placebo, recognizing that the
16 volanesorsen group in CS16 comprises a mixture of
17 exposure to 300 milligrams volanesorsen weekly and
18 every other week due to a protocol amendment.

19 Additional safety data was provided from
20 patients participating in the open-label extension
21 study, CS7.

22 CS7 included patients with FCS who were

1 treated with placebo and volanesorsen in the parent
2 studies CS6 and 16 as well as newly identified
3 patients with FCS. Therefore, CS7 includes
4 patients with variable durations of volanesorsen
5 exposure.

6 Serious adverse events from ongoing blinded
7 clinical trials in other patient populations were
8 also reviewed. Relevant events from these trials
9 will be discussed in this presentation.

10 This slide shows patient exposure to
11 volanesorsen and includes cumulative exposure for
12 patients participating in both the phase 3 parent
13 trials and extension studies. At the time of the
14 NDA submission, 126 patients were treated with
15 volanesorsen in phase 3 trials. 56 were adults
16 with FCS.

17 Of these 56 FCS patients, 26 patients had
18 over 180 days' exposure, 11 had greater than 365
19 days of exposure, and 1 patient had greater than
20 720 days of exposure to volanesorsen.

21 At the 4-month safety update, 25 additional
22 patients with FCS had been exposed to treatment

1 with volanesorsen, yielding a cumulative total of
2 81 patients with FCS exposed in phase 3 trials. Of
3 these, 23 have been treated for greater than 365
4 days and 5 have received treatment for greater than
5 720 days.

6 This diagram illustrates the disposition of
7 FCS patients who were randomized into the pivotal
8 trial, CS6, through the open-label study.

9 33 patients were treated with either placebo or
10 volanesorsen.

11 Over the 1-year study duration, 14 patients
12 in the volanesorsen group discontinued treatment,
13 mostly due to adverse events. Only 1 patient in
14 the placebo group discontinued treatment. Of the
15 19 patients who completed the study on
16 volanesorsen, 5 elected not to continue treatment.
17 While the reasons for not electing to participate
18 in the open-label trial were not systematically
19 collected, for 4 of the patients, there were
20 ongoing adverse events at the time of study
21 completion, including low platelet counts.

22 Fourteen patients treated with volanesorsen

1 in CS6 elected to participate in the open-label
2 extension study. Of these, an additional
3 5 patients discontinued, leaving only 9 out of the
4 original 33 patients as of the 4-month safety
5 update on volanesorsen.

6 Of the 9, only 1 remains on 300 milligrams
7 of volanesorsen weekly. Nearly all patients in
8 both the placebo and volanesorsen-treated groups
9 experienced at least 1 adverse event, although
10 there were a higher number of events reported in
11 the volanesorsen-treated versus placebo-treated
12 patients.

13 There were no deaths in the clinical program
14 and the incidence of serious adverse events was
15 similar or only slightly higher in the volanesorsen
16 group compared to the placebo group. However, a
17 substantial difference in treatment
18 discontinuations was observed in patients treated
19 with volanesorsen compared to patients treated with
20 placebo.

21 In the pivotal trial, 42 percent of patients
22 randomized to volanesorsen discontinued treatment

1 compared to 3 percent of placebo-treated patients.

2 The most common reason for treatment

3 discontinuation was due to adverse events.

4 In CS16, 20 percent of volanesorsen-treated

5 patients withdrew due to an adverse event, mostly

6 due to injection site reactions. There were also 2

7 of the 5 volanesorsen-treated patients listed as

8 other as the reason for discontinuation, which on

9 review of the narratives described 1 patient with a

10 platelet count less than 50,000 and the other

11 meeting a stopping rule for proteinuria.

12 The most common adverse drug reactions were

13 events at the injection site across the phase 3

14 trials. Injection site reactions will be discussed

15 later in this presentation. Excluding injection

16 site events, the most common adverse events,

17 defined here as occurring in at least 10 percent of

18 volanesorsen-treated patients and greater than

19 placebo are shown in this graph.

20 In adult patients with FCS, the most common

21 adverse events were related to low platelet counts,

22 bleeding events such as epistaxis and petechiae,

1 constitutional symptoms such as fatigue,
2 gastrointestinal events such as abdominal pain,
3 nausea, and vomiting, and musculoskeletal symptoms
4 of arthralgia and myalgia.

5 A similar or slightly higher proportion of
6 volanesorsen-treated patients reported a serious
7 adverse event. Important serious treatment events
8 included thrombocytopenia, serious events of
9 hypersensitivity, and events associated with flu-
10 like reactions.

11 As mentioned earlier, volanesorsen-treated
12 patients discontinued due to adverse events and
13 more frequently than placebo-treated patients. In
14 the pivotal trial, 9 volanesorsen-treated patients
15 compared to no placebo-treated patients
16 discontinued due to an adverse event.

17 The most common reason for discontinuation
18 was related to low platelet count followed by
19 fatigue. Many of the events resulting in treatment
20 discontinuation are symptoms or signs of specific
21 safety concerns associated with volanesorsen
22 treatment which will be discussed in more detail.

1 These safety topics include the following,
2 injection site reactions, immunogenicity and
3 hypersensitivity, renal and hepatic events, and
4 lastly thrombocytopenia and risk of bleeding.

5 The first safety topic is injection site
6 reactions. Adverse events at the injection site
7 were the most common event reported in all phase 3
8 trials. In study CS6, no placebo patient reported
9 an injection site reaction. And 79 percent of
10 volanesorsen-treated patients reported almost 500
11 individual events.

12 The average number of injections in the
13 pivotal trial before the first reported injection
14 site reaction was 6 with a range of 1 to 34
15 injections. The median time to resolution of these
16 events was 8 days. Skin discoloration was noted in
17 20 to 30 percent of patients at the injection site
18 in phase 3 trials.

19 Five patients in CS6 and 16 patients in CS16
20 had discoloration events at the injection site that
21 had not resolved. 1 patient in the pivotal trial
22 discontinued due to an injection site reaction and

1 is discussed next. This patient with FCS was
2 randomized to volanesorsen, 300 milligrams per
3 week, and received a total of 13 doses. An adverse
4 event at the injection site was reported on study
5 day 1.

6 In total, this patient experienced 25
7 adverse events at the injection site. No
8 concomitant medications were administered for these
9 injection site reactions. The patient discontinued
10 from volanesorsen treatment due to injection site
11 reactions and fatigue, but continued in the study
12 and completed follow-up in study week 52.

13 Hyperpigmentation, loss of sensitivity, and
14 skin depression at the injection site were ongoing
15 at the follow-up visit. These photos were taken
16 approximately 4 months after the last
17 administration of volanesorsen.

18 The next topic is immunogenicity and
19 hypersensitivity. Volanesorsen antidrug antibodies
20 were analyzed at baseline approximately every 4 to
21 13 weeks. Of the 33 volanesorsen-treated patients
22 in the pivotal trial, 11 patients or 33 percent

1 tested positive for antidrug antibodies. The
2 median time of onset was approximately 6 months.

3 In general, positivity was persistent from
4 onset through the last evaluation. Development of
5 antidrug antibodies did not appear to affect
6 triglyceride levels or platelet count over time for
7 the 11 patients positive for antidrug antibodies in
8 the pivotal trial.

9 Review of a serious hypersensitivity
10 reaction of serum sickness and anaphylaxis noted a
11 potential association with development of anti-
12 volanesorsen antibodies, which will be discussed in
13 a moment.

14 Overall, there was a higher proportion of
15 volanesorsen-treated patients compared to placebo-
16 treated patients reporting a hypersensitivity event
17 in both CS6 and CS16. Within the volanesorsen
18 treatment group, there was a slightly higher
19 proportion of ADA-positive patients compared to
20 ADA-negative patients reporting an event. However,
21 the number of patients are small.

22 In both CS6 and 16, erythema was reported by

1 the largest number of patients. Although not
2 classified as a serious adverse event by the
3 applicant, a patient in CS6 developed itching and
4 erythema extended to whole body surface after
5 3 months of dosing despite the use of oral and
6 topical antihistamines for previous injection site
7 reactions.

8 The persistent erythema led to an ER visit,
9 discontinuation of volanesorsen, dermatology
10 consultation, treatment with steroids,
11 antihistamines, and eventually cyclosporin.

12 Two serious cases of hypersensitivity
13 occurred in non-FCS patients and will be discussed
14 next. The first case is a 47-year-old man with
15 hypertriglyceridemia, randomized at 300 milligrams
16 of volanesorsen weekly. After his 18th and
17 19th doses, the patient developed flu-like
18 symptoms.

19 Volanesorsen was held. 19 days after his
20 last dose of study drug, the patient reported fever
21 of 104 degrees Fahrenheit and pain coincident with
22 the development of high positive anti-volanesorsen

1 antibody titers which peaked to 25,000.

2 The patient was started on high-dose
3 prednisone. A rheumatologist diagnosed this
4 patient with serum sickness.

5 The second case is from an ongoing clinical
6 trial in a different study population. This
7 patient while on volanesorsen, 300 milligrams per
8 week, developed vomiting, nausea, muscle aches
9 within 12 hours of dosing, starting with his 17th
10 dose.

11 Within 5 minutes of his 25th dose, the
12 patient experienced an event described as
13 anaphylaxis that required emergent administration
14 of epinephrine. The patient recovered from the
15 event and discontinued treatment.

16 This patient had been negative for anti-
17 volanesorsen antibodies and then converted to
18 positive, which were present at the time of the
19 anaphylactic reaction.

20 Flu-like reactions were events of interest
21 and defined by the applicant as either flu-like
22 illness, or pyrexia, or feeling hot, or body

1 temperature increased plus at least 2 of the
2 following symptoms, chills, myalgia or arthralgia
3 starting on the day of injection or the day after.

4 Case report forms did not prospectively ask
5 about each of these symptoms. Therefore, patient
6 and investigator would have had to report up to 3
7 signs and symptoms as adverse events within a
8 narrow time window to meet the definition for a
9 flu-like reaction.

10 This approach may underestimate the number
11 of patients with flu-like symptoms associated with
12 volanesorsen treatment. Therefore, an analysis was
13 conducted using a more sensitive definition of flu-
14 like reaction defined as reporting any of the
15 following events, starting on the day of injection
16 or next.

17 The results of both analyses are shown in
18 this table. Using a stricter definition of flu-
19 like reaction, only 2 in each of the phase 3
20 studies, 2 patients in each of the phase 3 studies
21 met the criteria.

22 Using the more sensitive FDA definition,

1 additional patients reported symptoms suggestive of
2 a flu-like reaction with volanesorsen
3 administration. The next safety topic to consider
4 are renal-related events.

5 Serious events of renal toxicity have been
6 associated with other antisense oligonucleotides
7 and, in the volanesorsen non-clinical program,
8 there was accumulation of drug in the kidney of
9 non-human primates with resulting tubular
10 vacuolation and proteinuria at clinical exposures.

11 In CS6, there were a small number of renal-
12 related adverse events reported, which mostly
13 reflected changes in laboratory values that were
14 transient and mild.

15 There was 1 case of acute kidney injury, but
16 it was temporally associated with acute diarrheal
17 illness and hypotension and it resolved with volume
18 resuscitation. There were 4 patients who had at
19 least 1 modest increase in creatinine, but which
20 exceeded 0.3 milligrams per deciliter or 50 percent
21 above baseline.

22 In CS16, 2 volanesorsen-treated patients met

1 renal-related stopping rules. 1 was for worsening
2 proteinuria from a baseline 242 milligrams per day
3 to approximately 1,500 milligrams per day after
4 approximately 3 months of treatment.

5 Although this patient had type II diabetes
6 and proteinuria at baseline, there was no clear
7 explanation for such an increase over this short
8 duration. The other patient met a stopping rule
9 for increased creatinine, but was able to continue
10 in the study after a temporary treatment pause.

11 A higher incidence of renal-related adverse
12 events was reported in CS16, 16 percent of
13 volanesorsen-treated patients versus 8 percent of
14 placebo, but none were serious. In summary, there
15 is no clear evidence for nephrotoxicity, including
16 immune-mediated etiologies.

17 A significant limitation of this program was
18 that proteinuria was not well quantified since
19 urine creatinine was not measured. Therefore, it
20 is possible that volanesorsen has an adverse effect
21 on the kidney that may have gone undetected to
22 date.

1 Given this limitation as well as the small
2 safety database, continued monitoring for a
3 potential renal adverse effect is warranted.

4 The next safety topic for discussion are
5 hepatic-related events. Small numbers of patients
6 treated with volanesorsen were noted to exceed
7 safety thresholds for ALT and AST elevations in CS6
8 and CS16. 2 volanesorsen-treated patients in study
9 CS16 met a stopping rule related to elevations in
10 liver enzymes.

11 One of these patients is depicted in this
12 slide. Her lab values over time for ALT are shown
13 in gold and AST in purple. After receiving 4 doses
14 of volanesorsen, the patient's ALT was 8 times the
15 upper limit of normal and AST was 10 times the
16 upper limit of normal. Bilirubin was within normal
17 limits.

18 No alternative etiology was determined.
19 After discontinuation of volanesorsen, liver
20 enzymes returned to baseline. In general,
21 elevations in liver enzymes were noted in a small
22 group of volanesorsen-treated patients which

1 resolved with discontinuation of treatment.

2 Association with volanesorsen cannot be
3 definitively ruled out. There were no cases of
4 Hy's Law, an indicator of drug-induced liver injury
5 noted with volanesorsen treatment.

6 The last safety topic is thrombocytopenia
7 and the risk of bleeding. This table below
8 describes the changes to platelet monitoring and
9 volanesorsen dosing as the clinical safety signal
10 of volanesorsen-induced thrombocytopenia emerged.
11 Please note the last column refers to amendments to
12 platelet monitoring and treatment discontinuation
13 that occurred after the last patient in the pivotal
14 trial had been dosed and impacted patients in the
15 ongoing open-label study.

16 Over time, the frequency of platelet
17 monitoring increased from 4 to 6 weeks to weekly.
18 The threshold for permanent discontinuation of
19 study drug became more stringent. The number of
20 dose re-challenges were limited and the dose
21 interval for volanesorsen was changed to every
22 other week for platelet counts that fell below

1 100,000.

2 This figure shows all platelet measurements
3 over time for the placebo group in blue and the
4 volanesorsen group in red for the pivotal trial.
5 The average baseline level of platelets in CS6 was
6 228,000 and 215,000 in the placebo and volanesorsen
7 groups respectively.

8 Two types of platelet reduction have been
9 observed with volanesorsen treatment. The first is
10 exhibited by the gradual decline noted in platelet
11 count of approximately 30 percent on average within
12 the first 6 months.

13 However, this description does not fully
14 characterize the clinically significant platelet
15 reductions observed with volanesorsen treatment.
16 Individual volanesorsen-treated patients
17 experienced a second type of platelet reduction
18 noted for rapid, severe decreases in platelet
19 count.

20 The number and percentage of patients with
21 nadir platelet count meeting categorical thresholds
22 at any time post-baseline are described in the

1 table below for patients in the phase 3 trials.

2 It is notable that, although the applicant
3 has presented data, patients with FCS have
4 significant variability in platelet count,
5 suggesting that significant thrombocytopenia may
6 occur as part of the natural history of the
7 disease.

8 In CS6, a 52-week randomized placebo-
9 controlled trial of patients with FCS, the
10 incidence of thrombocytopenia was substantially
11 higher among volanesorsen-treated patients than
12 placebo-treated patients.

13 Please also note that, as of the 4-month
14 safety update, there were 7 patients in the phase 3
15 trials that experienced a platelet nadir of less
16 than 50,000, 3 of whom had platelet counts less
17 than 25,000 for grade 4 thrombocytopenia.

18 This table does not include 2 additional
19 patients with platelet counts less than 50,000.
20 One case occurred in the phase 2 dose-finding study
21 and another case occurred after the 4-month safety
22 update cutoff.

1 Overall, there were 9 patients, 8 of whom
2 were patients with FCS with a platelet count less
3 than 50,000. The lowest platelet count ranged
4 between 8,000 and 49,000. 8 of these patients are
5 represented in this slide, as these patients had
6 experienced the event by the 4-month safety update.

7 The 9th patient was reported in February of
8 this year as a 15-day safety report. This event of
9 thrombocytopenia was reviewed as part of the
10 volanesorsen application and is included in this
11 discussion.

12 No patients had a major clinical bleeding
13 event, although 4 had minor clinical bleeding
14 events such as epistaxis and petechiae as
15 represented by the red triangle. The time to onset
16 from the start of volanesorsen to a count below
17 50,000 was highly variable, with a range of 51 to
18 300 days.

19 All patients recovered with discontinuation
20 of volanesorsen and in 6 patients with
21 administration of steroids, including 1 patients
22 who also received IVIg. 2 patients were re-

1 challenged with weekly volanesorsen dosing.

2 Patient D was able to maintain a platelet
3 count greater than 100,000. However, patient G had
4 a second platelet nadir less than 50,000 when re-
5 challenged with volanesorsen. In 3 patients,
6 patient E, F, and the latest case that is not
7 included on this slide, switching the frequency of
8 volanesorsen dosing to every other week did not
9 result in stabilization of platelet count.

10 Lastly, under enhanced platelet monitoring,
11 which included biweekly monitoring of platelet
12 count and dose adjustment, which was implemented
13 when patient A and B experienced a platelet count
14 less than 25,000, there have been an additional
15 4 patients in the ongoing open-label trial with
16 platelet counts less than 50,000, including
17 2 patients with platelet nadir of 15,000 and 17,000
18 respectively.

19 One of these patients was the most recently
20 reported case. This is a graphical profile of the
21 9th patient. The green line and blue dots
22 represent platelet counts from the central and

1 local labs respectively. The pink line represents
2 triglyceride levels.

3 The vertical lines represent either placebo
4 or volanesorsen administration. This patient with
5 FCS and no history of pancreatitis was randomized
6 to placebo in CS6. She enrolled in the open-label
7 extension study and started on volanesorsen, 300
8 milligrams per week.

9 She was switched to every-other-week dosing
10 due to a low platelet count. The patient
11 administered a dose of volanesorsen despite a
12 previous low platelet count of 69,000. Her
13 platelet count dropped to 17,000. The patient
14 received steroid therapy and the platelet count
15 rebounded. The patient did not report any clinical
16 bleeding.

17 Despite the patient and investigator,
18 complying with the protocol-directed platelet
19 monitoring at a minimum weekly, a treatment pause
20 did not occur and the patient was dosed. Grade 4
21 thrombocytopenia occurred approximately 300 days
22 after starting treatment with volanesorsen.

1 The proposed platelet monitoring and dose
2 adjustment may not prevent precipitous drops in
3 platelet count. And it is unknown if this
4 monitoring strategy will be able to quickly
5 identify patients with very low platelet counts and
6 intervene before a serious bleeding event occurs in
7 a real-world setting.

8 Thus far, investigations into the mechanism
9 of volanesorsen-induced thrombocytopenia are
10 inconclusive.

11 In addition to platelet counts, the
12 incidence of clinical bleeding was evaluated in the
13 pivotal trial. In an FDA analysis of the pivotal
14 trial, after excluding bleeding events at the
15 injection site and terms that only related to a
16 laboratory value, there was still a higher
17 proportion of volanesorsen-treated patients with
18 clinical bleeding compared to placebo with the most
19 frequent bleeding events being epistaxis and
20 petechiae.

21 This slide summarizes the clinical bleeding
22 events by the lowest previous platelet count. It

1 is of concern that clinical bleeding occurred for
2 most patients above 75,000, a value where one would
3 not expect spontaneous bleeding, suggesting a
4 possible effect on platelet function rather than
5 only platelet number.

6 To date, an assessment of platelet function
7 in FCS patients exposed to volanesorsen has not
8 been conducted. The use of anticoagulant and/or
9 antiplatelet medication in bleeding events was also
10 evaluated.

11 Patients who were taking these concomitant
12 drugs were more likely to experience bleeding in
13 both volanesorsen and placebo groups than patients
14 who were not taking them. An analysis for an
15 interaction between volanesorsen and antiplatelet
16 anticoagulants with respect to bleeding events was
17 not significant, but the small number of events
18 preclude definitive conclusions.

19 The applicant has proposed a new dosing
20 regimen for volanesorsen based on platelet count
21 and body weight in an attempt to reduce the risk of
22 severe thrombocytopenia and bleeding with

1 volanesorsen treatment.

2 Dr. Yunzhao Ren will now discuss the
3 applicant's proposal.

4 **FDA Presentation - Yunzhao Ren**

5 DR. REN: Good morning. My name is Yunzhao
6 Ren, the clinical pharmacology reviewer of
7 volanesorsen. I'll first introduce the PK
8 characteristics of volanesorsen followed by
9 applicant's dose selection rationale for phase 3
10 studies and, last, I will spend some time
11 discussing applicant's proposed dosing regimen
12 adjustment to mitigate the increased risk for
13 severe thrombocytopenia.

14 The absolute bioavailability of
15 volanesorsen, 300 milligrams subcutaneous
16 injection, is approximately 80 percent. Although
17 the study dosing regimen is once weekly, about
18 95 percent of the weekly systemic exposure is
19 concentrated on day 1.

20 Volanesorsen has a maximum concentration or
21 Cmax is reached approximately 4 hours post-dose.
22 And at the end of the dosing day, volanesorsen mean

1 plasma concentration drops to about 5 percent of
2 the mean Cmax value.

3 Afterwards, volanesorsen plasma
4 concentration decreases slowly to about 1 percent
5 of the mean Cmax value at the end of the week.

6 Animal studies indicate that the initial
7 elimination phase of volanesorsen is mostly due to
8 the wide distribution through the peripheral
9 tissues. In the human relevant animal model,
10 cynomolgus monkey, the hepatic concentration is
11 about 60-fold higher than the plasma peak
12 concentration.

13 In a mass balance study in rat, it shows
14 that the drug exposure in bone marrow is
15 approximately 200-fold higher than the exposure in
16 plasma.

17 Next part, I will discuss applicant's dose
18 selection rationale of volanesorsen. Phase 2 study
19 CS2 was the only dose-ranging study conducted in
20 volanesorsen clinical program. It was a randomized
21 double-blind placebo-controlled parallel group
22 dose-ranging study in adults with severe or

1 uncontrolled hypertriglyceridemia.

2 The inclusion criteria for fasting
3 triglyceride serum concentration at screening were
4 at least 440 milligrams per deciliter if patients
5 were not on triglyceride-lowering therapy or at
6 least 225 milligrams per deciliter if patients were
7 on a stable well-controlled dose of fibrate or
8 patients with FCS diagnosis.

9 Enrolled patients were divided into 4
10 groups, a once weekly treatment for 13 weeks.
11 Group 1 and 2 were on once-weekly monotherapy of
12 placebo, of volanesorsen, 100, 200, or 300
13 milligram. Group 3 was a combination therapy of
14 fibrate plus placebo or volanesorsen, 200 or 300
15 milligram. Group 4 was a proof of concept, open-
16 label group of 3 patients with FCS diagnosis.

17 apoC-III is the target protein of
18 volanesorsen. Dose-ranging studies demonstrate
19 that, following 13 weeks once-weekly treatment,
20 there is a dose-dependent and time-dependent
21 reduction of apoC-III serum mean concentration from
22 the baseline in patients on volanesorsen

1 monotherapy.

2 apoC-III reduction status date appears to
3 have reached approximately at week 13. Similarly,
4 a dose-dependent and time-dependent reduction of
5 triglyceride serum mean concentration from baseline
6 was also observed in the same patient population.

7 Triglyceride reduction steady state appears
8 to have been reached approximately at week 9. In
9 addition, a dose-dependent and time-dependent
10 reduction of mean platelet count from the baseline
11 was observed in the same study for all 4 treatment
12 groups.

13 However, the steady state of mean platelet
14 reduction appeared to not have reached at week 13
15 in this study. Of note, in this study, 1 patient
16 with FCS experienced severe thrombocytopenia with
17 platelet count reduced to less than 50,000 per
18 microliter on the second day after week 13 dose,
19 which is the last dose.

20 At an end of phase 2 meeting, the applicant
21 proposed a plan to carry 300-milligram once-weekly
22 dosing regimen into phase 3 studies based on the

1 results from study CS2. However, FDA commented
2 that applicant's development program to date was
3 extremely limited and it took a substantial risk
4 proceeding with just one dosing level into phase 3
5 studies.

6 Next part, I will discuss the assessment of
7 applicant's proposed dosing regimen adjustment to
8 mitigate the increased risk for severe
9 thrombocytopenia. The discussion will start with
10 more observations from phase 3 studies.

11 Consistent with study CS2, phase 3 study CS6
12 also demonstrated a time-dependent mild to moderate
13 reduction of mean platelet count from baseline in
14 patients with FCS upon 300 milligrams of
15 volanesorsen once-weekly treatment.

16 In study completers, as shown in this
17 figure, a steady state of mean platelet count was
18 with approximately 37 percent reduction from
19 baseline, appeared to have reached at about week 32
20 in the volanesorsen treatment group.

21 At the steady state, the absolute mean value
22 of platelet count was approximately 130,000 to

1 140,000 per microliter, which is lower than the
2 lower limit of normal range of platelet count.

3 Also in the volanesorsen treatment group,
4 13 out of 19 study completers, two thirds of them
5 had at least one platelet count reduced to lower
6 than 100,000 per microliter during this study.

7 However, other than time-dependent mild to
8 moderate reduction of mean platelet count from
9 baseline, we noticed there was another type of
10 platelet reduction in phase 3 studies. As shown in
11 this slide, 7 more patients experienced severe
12 thrombocytopenia in phase 3 studies by cut-off data
13 of 4-month safety update other than the first
14 patient H from study CS2, who had low platelet
15 count at baseline.

16 The other 7 patients had normal platelet
17 count at baseline. The hallmark of the platelet
18 reduction pattern in these 7 patients is a rapid
19 precipitous decline of platelet count in short
20 period of time.

21 Some patients had platelet count dropped
22 from normal range to less than 50,000 in just one

1 month, with maximal reduction rate of about 45,000
2 per week. In addition, the time to onset in these
3 patients tends to occur at an earlier time point.

4 One patient experienced the severe
5 thrombocytopenia as early as on day 51 and the
6 majority of these patients first experienced
7 thrombocytopenia in less than 14 weeks. Therefore,
8 it is fair to separate the platelet reduction
9 pattern of these severe cases from the time-
10 dependent slow platelet reduction pattern observed
11 from the previous slides.

12 We tend to define the slow reduction pattern
13 as type 1 reduction and the fast severe reduction
14 pattern as type 2 reduction. This concept has been
15 introduced by FDA for certain second-generation
16 antisense oligos in a paper published last year,
17 which is listed in this table.

18 When we summarized these 8 patients here, we
19 noticed that 7 out of 8 patients are FCS patients,
20 indicating that FCS patients upon volanesorsen
21 treatment could be a potential risk factor of
22 severe thrombocytopenia. On the other hand,

1 generally there's no gender susceptibility to the
2 severe thrombocytopenia and the distribution of age
3 and body weight in these 8 patients are quite wide.

4 With the concept of 2 types of platelet
5 reduction introduced, next I will discuss the
6 relationship between baseline body weight, drug
7 exposure, and nadir platelet counts.

8 The common ground shared by FDA and the
9 applicant is the apparent relationship between body
10 weight and nadir platelet count observed from two
11 randomized phase 3 studies by considering that many
12 patients discontinued the studies and that nadir
13 platelet values could be overestimated due to the
14 short treatment period.

15 The relationship is quite impressive. The
16 labeled points in this part are 4 patients who
17 experienced type 2 severe thrombocytopenia in these
18 two studies. And 3 out of these 4 patients are
19 outside a 95 percent prediction interval of the
20 linear model, indicating that this apparent body
21 weight nadir platelet count relationship may not
22 well predict type 2 severe thrombocytopenia cases.

1 On the other hand, I'm not saying that type
2 1 platelet reduction is not important, as under
3 certain extreme conditions such as this circled
4 patient I, who was a 71-year-old female with body
5 weight of only 37 kilograms, experienced 75 percent
6 reduction of platelet count from baseline, down to
7 50,000 per microliter at week 41.

8 This case represents a typical extreme case
9 of type I platelet reduction and can be captured by
10 this body weight nadir platelet relationship. In
11 conclusion, the body weight nadir platelet
12 relationship further implies the existence of two
13 types of platelet reduction and type 2
14 thrombocytopenia could not be reliably predicted by
15 the body weight.

16 The applicant proposed a dosing regimen
17 adjustment plan for mitigation of severe
18 thrombocytopenia events regardless of the platelet
19 reduction types. The first criterion of this plan
20 is based on the baseline of platelet count in which
21 patients with baseline platelet count less than
22 140,000 per microliter will be excluded from

1 receiving volanesorsen treatment.

2 Second, the applicant proposed a once-weekly
3 to biweekly dosing regimen switch in patients with
4 lower platelet count based on the platelet
5 monitoring results. And all the patients with body
6 weight less than 70 kilograms were supposed to
7 switch to the biweekly dosing regimen no later than
8 month 3.

9 Third, patients should stop volanesorsen
10 treatment when platelet count drops to below 75,000
11 per microliter. And they can be re-challenged by
12 volanesorsen after their platelet count recovered.

13 Of note, the proposed dosing regimen
14 adjustment was not pre-specified and well
15 investigated in volanesorsen clinical studies.
16 From a clinical pharmacology perspective, a dosing
17 regimen adjustment based on intrinsic factors such
18 as body weight should be justified by the rationale
19 that the intrinsic factor is associated with drug
20 systemic exposure and that drug systemic exposure
21 is associated with adverse events.

22 Compared to the body weight nadir platelet

1 plot, the relationship between body weight and the
2 volanesorsen clearance is weaker and shallower.
3 Here, the results are from population PK dataset,
4 which included 6 clinical studies.

5 For those of you who are not familiar with
6 drug clearance, drug clearance is the reciprocal of
7 drug exposure. The lower the value of drug
8 clearance, the higher the systemic drug exposure.

9 Five patients experienced severe
10 thrombocytopenia and with their clearance value
11 available are plotted here as red points. If 70
12 kilograms is chosen as a cut-off of which the
13 predicted clearance is 1.62 liter per hour, you
14 will see those 5 patients are randomly distributed
15 in all 4 quadrants, indicating that 70 kilograms
16 may not be an optimal body weight cutoff.

17 In addition, 3 of these 5 patients have drug
18 clearance higher than the population median value,
19 indicating that their systemic drug exposure is
20 lower but not higher than population median
21 exposure. Therefore, it appears that there's no
22 clear relationship between higher drug exposure and

1 type 2 severe thrombocytopenia events.

2 On the other hand, let's go to that extreme
3 case of type 1 platelet reduction, patient I. The
4 clearance of this female weighing 37 kilograms is
5 1.38 liter per hour. The case is well captured by
6 this linear model, indicating body weight-based
7 dose or dosing regimen adjustment may be helpful
8 mitigating extreme cases of type 1 platelet
9 reduction.

10 However, selection of non-optimal body
11 weight cutoff for mitigation of extreme type 1
12 platelet reduction is tricky. As the body weight
13 clearance relationship is shallow, for example, the
14 clearance of patient I is only 22 percent lower
15 than the population median clearance.

16 Of note, the estimated intrasubject
17 variability of volanesorsen clearance is about 20
18 percent. This figure directly demonstrates the
19 relationship between volanesorsen clearance and
20 nadir platelet counts. Similarly, the relationship
21 is weaker, indicating that there are some factors
22 other than drug exposure that contribute to the

1 apparent relationship between body weight and nadir
2 platelet counts.

3 Of note, 3 out of 4 patients experienced
4 type 2 severe thrombocytopenia in 2 phase 3
5 studies, also appear as outliers in this plot.

6 In conclusion, generally, there are
7 relationships between the baseline body weight,
8 drug exposure, and nadir platelet counts in
9 patients with severe hypertriglyceridemia,
10 including patients with FCS.

11 These relationships may be helpful to
12 predict and therefore be used to mitigate extreme
13 type 1 platelet reduction cases based on the
14 baseline body weight, though the appropriate cut-
15 off of the body weight and the mitigation methods
16 need to be further optimized.

17 On the other hand, all the results
18 consistently demonstrate that the relationships
19 between body weight, drug exposure, and nadir
20 platelet counts could not reliably predict type 2
21 severe thrombocytopenia cases, as most of them are
22 outliers of the predictive model.

1 Of note, close to 90 percent of the observed
2 severe thrombocytopenia cases in volanesorsen
3 clinical development program belongs to type 2,
4 severe type 2 platelet reduction.

5 Next couple slides will switch the topic to
6 the assessment of applicant's mitigation proposal,
7 which is the weekly to biweekly dosing regimen
8 switch. The regimen switch assessment will come
9 from 3 different angles; the first, the effect of
10 regimen switch in patients weighing less than
11 70 kilograms with normal platelet counts; second,
12 the effect of regimen switching type 2 severe
13 thrombocytopenia cases; and third, the re-challenge
14 of biweekly treatment of the platelet count
15 recovery.

16 Study CS16 has 3 subjects weighing less than
17 70 kilograms with normal platelet counts and they
18 switched from weekly to biweekly regimen post-week
19 13. As shown here, platelet count from patient J
20 continued a reduction trend after biweekly dosing
21 regimen switch, whereas the other 2 patients'
22 platelet count appeared stabilized post-switch.

1 However, none of the 3 patients demonstrated
2 a clear rebound trend of platelet count after
3 biweekly dosing regimen switch. And biweekly
4 dosing regimen switch does not appear to mitigate
5 the severe thrombocytopenia in some patients as
6 shown in this figure again.

7 By cutoff date of 4-month safety update,
8 there were 2 patients from open-label study CS7 who
9 experienced severe thrombocytopenia after the
10 dosing regimen switch from once weekly to biweekly.
11 And the reason of regimen switch in these two
12 patients was the low platelet count.

13 In the previous presentation, Dr. Roberts
14 mentioned a third patient experienced severe
15 thrombocytopenia after the biweekly dosing regimen
16 switch and that was a recent event which is not
17 listed in this slide.

18 For the re-challenge of volanesorsen
19 treatment after recovery of platelet count,
20 although we do not have a case's re-challenge with
21 biweekly regimen, we do have a case re-challenge
22 with once-weekly regimen after the platelet count

1 recovered, as highlighted in this slide. Patient G
2 experienced the second thrombocytopenia event after
3 treatment re-challenged.

4 Here is the assessment of the biweekly
5 dosing regimen mitigation proposal. For patients
6 weighing less than 70 kilograms and with normal
7 platelet counts, the effect dosing regimen switch
8 from once weekly to biweekly after month 3 is
9 inconclusive based on the limited observations from
10 only 3 subjects.

11 Observed results suggest that the switch
12 from once weekly to biweekly dosing regimen does
13 not appear to mitigate the risk. And lastly, re-
14 challenge of volanesorsen after platelet recovery
15 is inconclusive. One FCS patient re-challenged
16 with once-weekly treatment triggered the second
17 thrombocytopenia event.

18 In conclusion, the relationship between body
19 weight, drug exposure, and nadir platelet counts
20 are generally helpful in prediction of extreme
21 cases of type 1 thrombocytopenia and therefore may
22 be used in mitigation of these cases.

1 However, the cutoff of body weight needs to
2 be optimized. In addition, we don't know which is
3 an optimal way to mitigate extreme cases of type 1
4 thrombocytopenia, I mean, by dose reduction or by
5 dosing frequency reduction. Here, the applicant
6 only proposed dosing frequency reduction mitigation
7 plan.

8 For note, there's only 1 dosing strength
9 available for the to-be-marketed volanesorsen drug
10 product. For type 2 severe thrombocytopenia, the
11 cases could not be reliably predicted by these
12 relationships. Therefore, reduction of drug
13 exposure may not be helpful in mitigation of the
14 type 2 severe thrombocytopenia as proved by some
15 cases that switch from weekly to biweekly regimen
16 could not prevent the event.

17 Further, from the observed results, we note
18 that the fact of biweekly regimen switch on
19 platelet count is inconclusive in patients weighing
20 less than 70 kilograms with general type 1 platelet
21 reduction.

22 Treatment re-challenge by weekly regimen

1 after platelet recovery is also inconclusive due to
2 lack of data. In general, applicant's dosing
3 regimen adjustment plan based on the baseline body
4 weight and platelet counts for mitigating severe
5 thrombocytopenia appears inadequate or minimal if
6 not optimal.

7 FDA acknowledged that the algorithm of
8 volanesorsen dose or dosing regimen adjustment is
9 still in the process of optimization by the
10 applicant, but at the current stage, an intensive
11 platelet monitoring plan appears clinically
12 critical.

13 This concludes my presentation and I
14 introduce our next speaker, Dr. Chapman, for
15 discussion of volanesorsen risk evaluation and
16 mitigation strategies.

17 **FDA Presentation - Ingrid Chapman**

18 DR. CHAPMAN: Good morning. My name is
19 Ingrid Chapman and I am a reviewer in the Division
20 of Risk Management. I'll be discussing the risk
21 evaluation and mitigation strategy considerations
22 for volanesorsen.

1 A risk evaluation and mitigation strategy or
2 REMS is a risk management plan that utilizes
3 strategies beyond labeling to ensure that the
4 benefits of a drug outweigh the risks. It is
5 designed to achieve specific goals to mitigate
6 risks associated with the use of the drug.

7 The FDA has the authority to require a REMS
8 pre-approval or post-approval. A REMS may include
9 any of the following elements; a medication guide
10 or patient package insert, a communication plan,
11 elements to assure safe use, which I will discuss
12 in more detail on the next slide, and an
13 implementation system.

14 A REMS must include a time table for
15 submission of assessments. The following are
16 requirements that may be included in a REMS with
17 elements to assure safe use, prescriber training
18 and/or certification, dispenser certification,
19 which may include pharmacies, practitioners, or
20 certain healthcare settings, where the product is
21 dispensed could be limited; for example hospitals;
22 documentation of safe use conditions prior to

1 dispensing, which may include laboratory testing,
2 patient monitoring, and a patient registry.

3 The following must be considered if the FDA
4 is contemplating elements to assure safe use. A
5 product can be approved only if an element to
6 assure safe use is put in place to mitigate the
7 risk. It cannot be excessively burdensome on
8 patient access to the drug considering patients
9 with serious or life-threatening disease and
10 patients who have difficulty accessing healthcare.

11 It must be similar to other products with
12 elements to assure safe use that have similar
13 serious risks and be designed to work with
14 established drug distribution, procurement, and
15 dispensing systems.

16 Now, I'd like to focus on the safety
17 concerns of volanesorsen for which a REMS is being
18 considered. As mentioned previously, the risk is
19 potential serious bleeding due to severe
20 thrombocytopenia. The specific concerns are that
21 the mechanism of the thrombocytopenia is unknown.

22 The timing and severity of the platelet

1 reduction is unpredictable and the impact of
2 volanesorsen and familial chylomicronemia syndrome
3 on platelet function is unknown. What do we aim to
4 accomplish with the risk mitigation for
5 volanesorsen?

6 The primary objectives are to educate
7 prescribers about the risk of potential serious
8 bleeding due to severe thrombocytopenia and
9 reinforce the need for patient counseling and
10 monitoring. We also want to support the patient's
11 desire to make informed decisions and continue to
12 support the REMS for the safe use of volanesorsen.

13 After reviewing the safety data for
14 volanesorsen, the FDA has developed the REMS goal
15 shown here. The goal is to mitigate the potential
16 risk of serious bleeding due to severe
17 thrombocytopenia associated with volanesorsen by
18 educating prescribers about the risk, counseling
19 patients about the risk, and enrolling all patients
20 in a REMS registry to further support long-term
21 safety and safe use of volanesorsen.

22 To accomplish the proposed goal, we

1 recommend the following elements to assure safe
2 use. I'll explain these in greater detail based on
3 the safety considerations and requirements for each
4 of the REMS participants.

5 First, I'll discuss the prescriber
6 requirements. Prescribers must complete prescriber
7 training and subsequently enroll in the REMS
8 program. Prescribers must enroll patients in the
9 REMS program using the patient-prescriber agreement
10 form.

11 Prescribers also have to complete and submit
12 a patient status form every 90 days to the REMS
13 program. The patient status form is documentation
14 of patient monitoring and may collect information
15 about serious bleeds, significant declines in
16 platelet count, and treatment modification.

17 Regarding pharmacy requirements to dispense
18 volanesorsen, pharmacies must designate an
19 authorized representative and enroll in the REMS
20 program. The pharmacy must also verify prior to
21 dispensing that both the prescriber and patient are
22 enrolled in the REMS program.

1 Lastly, regarding patients' requirements,
2 prior to receiving volanesorsen, patients must
3 receive counseling from the prescriber, using the
4 patient prescriber agreement form and enroll in a
5 REMS program and REMS registry.

6 In summary, the FDA is proposing prescriber
7 certification and training, pharmacy or dispenser
8 certification, documentation of safe use conditions
9 via patient-prescriber agreement form at the time
10 of treatment initiation, routine patient monitoring
11 that is documented every 90 days using a patient
12 status form and enrollment of all patients in a
13 REMS registry.

14 Regarding the applicant-proposed REMS,
15 initially a communication plan-only plan REMS was
16 submitted. We had discussions with the applicant
17 regarding their proposal and they subsequently
18 submitted a REMS amendment on April 4th, 2018. The
19 applicant-proposed REMS now aligns with the FDA-
20 proposed REMS with the same elements to assure safe
21 use.

22 As the applicant presented earlier, they are

1 proposing additional activities beyond the REMS,
2 which includes a patient support program. While
3 the patient support program includes such
4 activities as nurse case managers providing patient
5 education and facilitating scheduling of laboratory
6 services, it is imperative to know that these
7 activities are voluntary on behalf of the
8 applicant.

9 Because these activities are outside of the
10 REMS, the FDA will not be able to enforce or assess
11 these activities. Additionally, because the
12 patient support program is voluntary, it may be
13 discontinued at any time without notifying the FDA.
14 In assessing the benefit-risk profile of
15 volanesorsen, please consider that the benefits
16 must outweigh the risks and must be sustained
17 without the applicant's proposed voluntary
18 activities.

19 We have attempted to strike a balance
20 between safety and burden, knowing that patients
21 should be monitored routinely. Our proposed REMS
22 can ensure prescribers are educated and patients

1 are aware of the risk and the need for frequent
2 monitoring.

3 However, there are limitations to the
4 proposal, one being that rapid and severe decreases
5 in platelets may not be prevented even with
6 compliance with rigorous monitoring and dose
7 modifications per the prescribing information.

8 The second limitation is that the proposed
9 REMS will not enforce monitoring as described in
10 the prescribing information. It's uncertain if the
11 burden associated with additional requirements
12 would add a greater degree of safety. We'd like to
13 hear the committee's thoughts on the proposed REMS.
14 This concludes my presentation. My colleague,
15 Dr. Roberts, will now return to wrap up the FDA
16 presentation.

17 **FDA Presentation - Mary Roberts**

18 DR. ROBERTS: I would now like to summarize
19 our conclusions regarding the benefits and risks of
20 volanesorsen, which are drawn from our
21 interpretation of the supporting evidence and
22 uncertainties of the data provided and are also

1 considered with the underlying condition familial
2 chylomicronemia syndrome in mind.

3 FCS is a rare autosomal recessive genetic
4 condition which affects 1 to 2 people per 1 million
5 individuals. Patients living with FCS are at risk
6 for pancreatitis, which is the most serious
7 consequence of this disease.

8 Patients with FCS also report other more
9 frequent symptoms which may be severe and
10 debilitating. Given that other forms of
11 hypertriglyceridemia may mimic some of the clinical
12 characteristics of FCS, an accurate and timely
13 diagnosis of FCS may be challenging.

14 Diet is currently the primary treatment
15 option for patients with FCS to manage elevated
16 triglycerides, but the restrictive nature of the
17 diet, while potentially effective is very difficult
18 to adhere to.

19 Safe and effective therapies are needed to
20 treat patients living with FCS. Following review
21 of the data provided, a significant reduction in
22 triglycerides was observed in patients with FCS

1 treated with volanesorsen. This is compelling
2 given the typical history of ineffective
3 triglyceride reduction with other triglyceride-
4 lowering medications.

5 However, when efficacy is established by its
6 effect on a surrogate endpoint, the magnitude of
7 direct clinical benefit typically remains
8 uncertain. Therefore, the benefit-risk assessment
9 must balance an uncertain direct clinical benefit
10 against the known and potential risks of the drug.

11 The risks associated with volanesorsen
12 include volanesorsen-induced thrombocytopenia of
13 unknown etiology which has the potential for
14 serious bleeding. Based on the information
15 provided we are unable to predict which patients or
16 when they will experience precipitous platelet
17 reductions.

18 Serious hypersensitivity events in patients
19 without FCS have occurred and there is a potential
20 connection between the emergence of anti-
21 volanesorsen drug antibodies and these events.

22 Injection site reactions occur in the

1 majority of patients. Skin discoloration at the
2 injection site may persist in some patients treated
3 with volanesorsen. Imbalances in flu-like
4 reactions and renal and hepatic biomarkers were
5 noted. No serious events of nephrotoxicity or
6 hepatotoxicity were observed. However, continued
7 monitoring is warranted.

8 There is also concern that the benefits and
9 risks of volanesorsen and feasibility of platelet
10 monitoring in children has not been studied. Going
11 forward, this will need to be addressed, given the
12 typical onset of symptoms in patients with FCS.

13 Lastly, the applicant has proposed an
14 approach for volanesorsen dosing and platelet
15 monitoring to address the potential risk of serious
16 bleeding with volanesorsen-induced
17 thrombocytopenia.

18 The applicant has proposed that the product
19 should be approved with a novel dosing regimen
20 based on body weight along with biweekly platelet
21 monitoring. This approach to dosing has not been
22 prospectively evaluated and it is not yet clear

1 that it would substantially improve the safety
2 profile for use of volanesorsen in this patient
3 population.

4 The proposed platelet monitoring recommends
5 every-two-week monitoring at a minimum for a
6 lifelong therapy, yet when enhanced platelet
7 monitoring was implemented in a clinical trial
8 setting with structured oversight, strict
9 monitoring, and dosing rules, 2 individuals
10 experienced severe thrombocytopenia with platelet
11 nadirs less than 25,000, including 1 who has been
12 monitored with weekly platelet counts.

13 Discussion of risk evaluation and mitigation
14 strategy options for this product have occurred in
15 parallel with the clinical review. It is unclear
16 whether the proposed strategies discussed thus far
17 would be effective in preventing serious bleeding
18 events in a post-market setting.

19 It is possible that a REMS may not be
20 sufficient to ensure safe use of volanesorsen
21 considering the data that are available at this
22 time.

Clarifying Questions to FDA

DR. WILSON: So that's the conclusion of the FDA presentation. Now, we have two things in the near future. One is to try to address some of the issues that the sponsor may be able to work on over lunch if we have any additional data requests, things that we haven't seen up to now.

Then we have a longer list that we're not going to get to before lunch and we'll come back to. So first, for those in the advisory committee, we're going to try to make very short things. You say I want to see this after lunch, so any requests along those lines?

Yes, please state your name and what you --

DR. KANE: Robert Kane. And one of my requests is to understand a little better the magnitude of the effect on triglycerides of weekly dosing versus every other week dosing. I did see that in CS16, I believe, where there was a switch.

DR. WILSON: So that's number one weekly versus other interval dosing. Dr. Ortel?

DR. ORTEL: I would like to see better

1 characterization of the thrombocytopenia. I'd like
2 to know if other cell lines are effective at the
3 same time. I'd like to know if there are
4 fragmented red cells or anything to suggest
5 microangiopathic hemolytic anemia. I'd also like
6 to know if all of the patients who dropped severely
7 were treated with prednisone or IVIg.

8 I'd consider that actually a risk that these
9 people are getting treated when we really don't
10 know what is happening.

11 DR. WILSON: I think that was the second
12 one. Any others? I had one and it's referent to
13 sponsor slide CO-58. If in fact there was an
14 outcome trial that was undertaken to prevent
15 pancreatitis, what would be the number of subjects
16 and how long might it take for persons or person
17 years to demonstrate that volanesorsen prevents
18 pancreatitis? And I would think that might be
19 available. Any others? Yes? Dr. Cuaresma?

20 MS. CUARESMA: Definitely not a doctor. I
21 am just a patient representative. I wish I was at
22 this point because my question is just a little bit

1 more general and I think it's because maybe I don't
2 understand.

3 But in the FDA, they went over; Dr. Ren had
4 went over a single dose lasting 300 milligrams, the
5 injection lasting 24 hours, which tells me that the
6 half-life of that dose doesn't last long.

7 So how does this affect the breakdown of the
8 chylomicrons until the next weekly dose? I guess I
9 don't understand or maybe somebody could articulate
10 that to me.

11 DR. WILSON: So as I understand it, you'd
12 like to know more about the effectiveness again of
13 a weekly dose versus a different interval than what
14 the effect is on chylomicrons in the plasma over
15 after that individual administration of a dose. Is
16 that the question?

17 MS. CUARESMA: Correct.

18 DR. WILSON: I think that relates to the
19 other questions about efficacy of weekly versus
20 other dosing versus -- and we've heard this earlier
21 for others as the dose versus interval changes.
22 Yes, one last one, perhaps? Dr. Kane, go ahead.

1 DR. KANE: Just to clarify, I think I
2 understood overall that epistaxis, bruising and
3 bleeding, was not useful as an antecedent
4 indication that the platelets were heading south.
5 And that typically occurred more at a higher
6 platelet level, 75,000 or so.

7 So I just wanted to understand there's no
8 useful clinical antecedent sign or symptom that the
9 platelets were going to go to the severe levels.
10 Thank you.

11 DR. WILSON: So Dr. Kane is summarizing what
12 many of us have said. Is antecedents prior to
13 epistaxis or prior to bleeding or prior to more
14 severe thrombocytopenia? We had elements of that,
15 but predicting it of course would be of a high
16 interest.

17 Then finally, Dr. Neaton, do you have
18 another?

19 DR. NEATON: A quick question; you enriched
20 the population for people with a history of
21 pancreatitis. Did you think about, in the design
22 of the study, given that enrichment strategy, what

1 fraction of people in the placebo group would
2 develop pancreatitis during follow-up?

3 DR. WILSON: From the sponsor, do you need
4 any clarifications for each of these questions that
5 we raised? And perhaps during the afternoon
6 session, after the open public hearing, you could
7 make an effort to respond to these queries.

8 DR. O'DEA: No clarification required.
9 Thank you.

10 DR. WILSON: So now we are going to adjourn
11 for lunch. And Latoya, what time should we be
12 back?

13 DR. BONNER: 1:06.

14 DR. WILSON: Shortly after 1:05. Thank you.

15 (Whereupon, at 12:07 p.m., a lunch recess
16 was taken.)

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A F T E R N O O N S E S S I O N

(1:05 p.m.)

Open Public Hearing

DR. WILSON: We're going to start in a minute or so. Good afternoon. Welcome to the open public hearing part of this program and the advisory committee reviews and recommendations, et cetera. And there's a preamble to this, so bear with me. I'm going to read this. It's a couple of paragraphs just so you understand what the open public hearing is.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency of the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you

1 may have with the sponsor, its product, and if
2 known, its direct competitors.

3 For example, this financial information may
4 include the sponsor's payment of your travel,
5 lodging, or other expenses in connection with your
6 attendance at the meeting. Likewise, FDA
7 encourages you, at the beginning of your statement,
8 to advise the committee if you do not have any such
9 financial relationships.

10 If you choose not to address this issue of
11 financial relationships at the beginning of your
12 statement, it will not preclude you from speaking.
13 And for the speakers, the FDA and this committee
14 place great emphasis in the open public hearing
15 process. The insights and comments provided by you
16 can help the agency and this committee in their
17 consideration of the issues before them.

18 That said, in many instances and for many
19 topics, there will be a variety of opinions. One
20 of our goals today is for this open public hearing
21 to be conducted in a fair and open way, where every
22 participant is listened to carefully, and treated

1 with dignity, courtesy, and respect. Therefore,
2 please speak only when recognized by the chair. In
3 advance, we thank you for your cooperation.

4 We have several speakers. I believe we have
5 13 on our list. Each one will generally have a
6 limit of 4 minutes and there will be a light
7 system. We will encourage them to wrap up if their
8 light comes on and they're going to go over time,
9 so we're ready to start.

10 Speaker number 1, please step to the podium
11 and, for each of you, introduce yourself, state
12 your name and any organization you are responding
13 for the record. Thank you. Go ahead.

14 MS. McCOY: Thank you. Good afternoon. My
15 name is Nicole McCoy and I live in North Carolina.
16 And I am very much willingly here on my own accord.
17 And I wanted to thank you from the get-go for the
18 opportunity to speak to you today about how I've
19 lived with FCS for the past 16 years.

20 I am one in a million, so this is your lucky
21 day. You get to meet me. But I have had FCS for
22 16 years, although undiagnosed for the first 10 and

1 it began when I got pregnant with my daughter.

2 I typically have an average triglyceride
3 level between 8 and 12, 13,000. And that's common
4 for me and that's been sustained for years. I've
5 also had 35 bouts of pancreatitis. And at this
6 point, I'm not willing to have another one. And
7 that's what I really want you to understand, that I
8 have lived with this disease and the extraordinary
9 burdens that it has, not just physically, the pain
10 is extraordinary, especially when you're having an
11 attack of pancreatitis.

12 But there are many other burdens. There are
13 financial burdens, social burdens, emotional, the
14 thought of, will today be another day where I go to
15 the hospital or will this 36th bout of pancreatitis
16 be my last one. It's very difficult to live under
17 those consequences every day, not just for me, for
18 my children, my husband, my family, my friends. It
19 really affects all of us.

20 I want you to truly understand that burden.
21 As a matter of fact, sometimes I think physically I
22 have the easy part because I lay in a hospital bed

1 and I just, you know, heal. It's my family who has
2 to endure every other challenge as I lay there
3 healing.

4 But I wanted you to think about a couple of
5 things that I've been through and kind of imagine
6 yourself in that position. My longest hospital
7 stay was 27 days, so I want you to imagine 27 days
8 without food or water. Your only nutritional
9 support is saline, pain medicine, potassium, iron,
10 magnesium, calcium, blood, transfusions,
11 antibiotics because of the infection on my
12 pancreas, and also the most difficult part of those
13 27 days was not seeing my children because there
14 was a ban in the hospital. Because of a flu
15 outbreak, they weren't allowed to see me.

16 To me, that's pretty devastating. To them,
17 it's devastating. And it has been just an enormous
18 challenge to deal with. There's a financial
19 burden. My family has struggled immensely. I was
20 a special education teacher and I had to resign two
21 years ago because of my illness. I was in the
22 hospital every 2 to 3 months.

1 Where I was a teacher in North Carolina, you
2 only get 10 sick days a school year. Well, every
3 other day, that one year, the last year I was in
4 the hospital 4 times. I had to pay a daily rate of
5 \$250 for every day over my 10 days of sick time.

6 That's a huge burden. My family has lost
7 our home. We've gone bankrupt and I'm not proud of
8 that. But when you have \$120,000 in medical bills,
9 even though I have insurance and I thought it was
10 really good insurance and I'm very grateful for it,
11 there's still a huge financial burden of 35
12 hospital visits for pancreatitis.

13 So my understanding of effective people is
14 to begin with the end in mind; seven habits of
15 highly effective people. And the end that I want
16 you to keep in mind is that I need your approval to
17 move forward with this medication.

18 The risks that you have discussed today are
19 far less than what I have gone through and will go
20 through even to the point of potentially death.
21 I'm not willing to do that. I am willing to take
22 those risks to embrace what may come with that

1 medication in the hopes that I may never have to go
2 into the hospital again,, not see my children,
3 maybe reduce the burden financially, reduce the
4 emotional anxiety that I do live with on a daily
5 basis, and I just appreciate your time and what you
6 are doing to help make the right decision. Thank
7 you so much.

8 DR. WILSON: Thank you. Thank you. I
9 remind the speakers, when the yellow light comes
10 on, on the podium, please try to start wrapping up
11 your presentation to stay on time and for all the
12 speakers to get their chance.

13 So speaker number 2, please come to the
14 podium, introduce yourself, and any organization
15 you represent.

16 MS. HARMON: Good afternoon. My name is
17 Mary Harmon from Hickory, North Carolina. I am
18 here today on my own to represent myself and all
19 those that suffer with a terrible disease, familial
20 chylomicronemia syndrome or FCS.

21 I have had a terrible struggle with this
22 disease since I was a teenager. I've had over 30

1 episodes of acute and chronic pancreatitis, 3
2 resulting in near-death experiences, in a coma, on
3 life support, filing for bankruptcy due to all the
4 medical bills, not being able to have children,
5 which resulted in divorce, and finally losing my
6 corporate job.

7 After being diagnosed genetically three and
8 a half years ago, I finally knew why I had been so
9 sick for most of my life. My triglycerides were
10 ranging from 5 to 10,000, constant pain in my left
11 side, xanthomas all over my body and in my eyes,
12 also severe brain fog and extreme fatigue.

13 Every day, I wondered if it would be my
14 last. I had never knew when an attack would occur
15 and was never able to make plans. Each day, I was
16 scared I would have to go to the ER and be treated
17 like a drug seeker or an alcoholic, treated like in
18 some way I had caused my own pain and suffering.

19 Once, I was cussed out by a nurse in the ER
20 after being diagnosed with acute pancreatitis. I
21 was screaming in pain and violently vomiting. The
22 next day, I was in a coma on life support. I had

1 to be shocked back to life in my hospital bed.

2 I was the first person in the world to go on
3 the study drug volanesorsen. Sure, there were side
4 effects from the drug, but having drug far
5 outweighs the pain and suffering of the acute
6 pancreatitis and near death experiences.

7 I wish I had been asked about those things
8 that matter to the FCS patient while I was in the
9 study. I had no hospitalizations while being on
10 volanesorsen for three years. I was the first
11 person in the world to finish the trial in three
12 years and came off drug in December 2017 as
13 required in the study. Waiting on the drug to be
14 approved for me to take again was a hard, long
15 waiting, nightmare.

16 On April 8th, a month ago, I was admitted
17 into ICU with acute pancreatitis for eight long
18 nights of suffering. This was the first time in
19 three years that I'd been hospitalized. Why?
20 Because I didn't have the drug.

21 Volanesorsen is my key for not getting
22 pancreatitis and having my life back. Volanesorsen

1 has saved my life into treatment where nothing else
2 is available. My triglyceride levels were down to
3 200, not the range of 5 to 10,000 prior to going on
4 drug.

5 Please, with a heartfelt plea, as someone
6 who actually died in the hospital and was brought
7 back to life, I need this medicine or otherwise I
8 will continue each day not knowing if I will be
9 alive tomorrow.

10 If I were your sister, brother, or mother,
11 father, or child, what would you do? Thank you for
12 your time and listening to my story.

13 DR. WILSON: Thank you very much. Next up,
14 speak number 3, introduce yourself and any
15 organization you represent.

16 MR. SAREMI: Thank you, Mr. Chair, ladies
17 and gentlemen, good afternoon. My name is Fred
18 Saremi and I'm here on my own to tell my story. I
19 was diagnosed with high lipid levels at age 30 and
20 it gradually increased to a level of about 2,600.
21 At times, it was as high as 8,000.

22 This resulted in frequent pancreatitis

1 episodes and trips to emergency rooms. I was
2 referred to many specialists and none of them knew
3 the cause or remedy for this disease. At this
4 point, pancreatitis episodes are recurring about
5 once every two weeks.

6 I'm sure you know that pancreatitis is one
7 of the most painful experiences a person can have.
8 The pain is comparable to a severe episode
9 associated in passing a kidney stone. It is
10 debilitating and disabling. I felt desperate,
11 alone, and hopeless.

12 As an FCS patient, I have lived with a very
13 unpredictable disease when pancreatitis could
14 strike at any time, even when I followed a very
15 restrictive low fat diet. I also had to cope with
16 frequent and severe vomiting and diarrhea on a
17 regular basis.

18 I recall many times laying on the bathroom
19 floor for many hours so that I could be close to
20 the toilet. In addition, I lived with the feeling
21 of perpetual fatigue, low energy level, and a sense
22 of mental fog.

1 All of these factors, a lot of anxiety,
2 fear, and a sense of isolation due to a highly
3 limited chance for social; this limited my social
4 interactions quite a bit; in addition frequent
5 absences because of pancreatitis. And it had a
6 very negative impact on my performance.

7 All of these elements had a profound impact
8 on my quality of life also. I was fortunate to
9 participate in the third phase of the new drug,
10 volanesorsen, and it worked great. During that
11 time, I didn't experience any episodes of
12 pancreatitis, vomiting, or diarrhea during the
13 course of the trial.

14 I still maintain a low-fat diet. I felt
15 great, like I never felt before. I had much more
16 energy, no more sense of fatigue, and no more
17 mental fog. I felt like there was a light at the
18 end of the tunnel. I could live like a more normal
19 life, like I used to. I wish I had been asked
20 these kind of questions in the quality of life
21 improvements in the questionnaires that have been
22 asked of me.

1 I feel the need for regular platelet testing
2 is a very small price to pay for all the great
3 benefits that this drug provides. Since I have
4 stopped taking this drug, my triglyceride levels
5 have been gradually climbing. I have experienced
6 some abdominal pain, but the big difference between
7 now and the past is that I can psychologically
8 handle it a lot better because I feel there is hope
9 and salvation coming.

10 It is like I hear the proverbial bugle of
11 the cavalry which is coming. It's coming around
12 the corner and it's going to save me. This drug
13 will provide hope and salvation to many of the FCS
14 patients I personally know.

15 I pray and highly urge FDA to approve this
16 drug because I believe that definitely this is a
17 life-changing medication. I appreciate your time.
18 Thank you and God bless.

19 DR. WILSON: Thank you very much. Next,
20 perhaps speaker number 4, please introduce yourself
21 and any organization you represent or that is
22 supporting you.

1 DR. CROSS: Hello, my name is Russ Cross and
2 I'm here on my own today to share my personal
3 experience with the rare disease, FCS. I'm a
4 pharmacist working as a pharmacy manager in Oregon.
5 When I was in my 20s, I was at a trade show. One
6 of the vendors asked me to volunteer to give some
7 blood to test out a new diabetes machine.

8 It came back with a reading of over 400. I
9 personally thought the machine was wrong. But I
10 went ahead and went to my doctor to see what was
11 going on. They drew my blood and had separated it
12 into a white layer and a red layer. My
13 triglyceride readings were over 2,500. My doctor
14 said basically they were unreadable.

15 The doctor diagnosed me with diabetes, but
16 he had no idea what to do with triglycerides other
17 than diet and exercise. Knowledge is everything
18 and to control my triglycerides was just something
19 I couldn't figure out.

20 My father had recently passed away from
21 pancreatitis due to high triglycerides and, because
22 of this, the symptoms of FCS have held me back from

1 pursuing many of my job goals, knowing that I may
2 not be healthy enough to maintain certain job
3 positions and titles.

4 After I turned 50, things got worse. One
5 day, I had to drive myself to the ER with severe
6 stomach pains. They drew my blood and, of course,
7 it separated into a white layer and a red layer
8 before it got to the lab. And it wasn't long
9 before I got the question, are you an alcoholic.

10 It doesn't take long or it doesn't take much
11 to make me mad, but that question does. I don't
12 drink and, when you don't drink, that question gets
13 old really fast. Eventually, they came back with a
14 diagnosis of pancreatitis. And my one and only
15 experience with this was with my father, so I just
16 figured I was dying.

17 Honestly, I didn't realize you could even
18 survive pancreatitis. I spent about a week in the
19 hospital before being released. After that, my
20 family doctor sent me to a lipid specialist who was
21 the first and only doctor to give my condition a
22 name.

1 After reviewing my situation, he diagnosed
2 me with familial chylomicronemia syndrome, which
3 even for a pharmacist is hard to say. I suffered
4 from pain, fatigue, memory loss, diabetes,
5 depression, fatty liver, kidney failure, and
6 anxiety. I believe these can all be tied to my FCS
7 condition.

8 Daily, I try to control my fat take. I
9 rarely if ever drink. There is a daily fight to be
10 good and reduce my fat content. Even doing that
11 does not ensure me a day away from my problems with
12 FCS.

13 For a long time, I've suffered with FCS
14 alone until my specialist asked me to attend a
15 patient advisory meeting for FCS in Portland,
16 Oregon. There, I met three other people with FCS
17 and this is where I really started to connect the
18 dots. It was nice to meet people with the same
19 condition so I could see why all this was
20 happening, like why I have brain fog and feel run
21 down and tired.

22 So much of my life, I've lived with symptoms

1 and conditions that doctors could not determine a
2 cause for. The most disturbing is the number of ER
3 visits due to stomach pain. Sharing my story with
4 other people who understand what I've gone through
5 helped me feel less anxious and less alone in a way
6 I haven't felt in years.

7 It was a game changer for both me and my
8 wife. So when I was given the opportunity to share
9 my story. I wanted to be the source of hope for
10 other people. I hope to inspire other people with
11 FCS not to give up and to keep seeking an effective
12 treatment and a better way of life.

13 I hope to help educate physicians and
14 healthcare communities so that they can be more
15 efficient at diagnosing FCS and I advocate for the
16 development of new and effective treatments that
17 will help us cope with this rare disease.

18 If my experience can help you gain a better
19 understand of what it's like to live with FCS, then
20 I feel like I've done something positive for myself
21 and others. Thank you.

22 DR. WILSON: Thank you very much. Next,

1 we'll have speaker number 5 please introduce
2 yourself and any organization that is helping to
3 sponsor you.

4 MS. SAREMI: Good afternoon. My name is
5 Lynne Saremi. And I'm here on my own behalf today
6 to speak to you from a caregiver's perspective.

7 I've been married for over 40 years to my
8 husband, who you met earlier, who was diagnosed
9 with FCS at the age of 30. In the early years
10 after his diagnosis, we made lifestyle changes such
11 as eating a low-fat diet, beginning a more vigorous
12 exercise program, and those changes kept his
13 triglycerides at a more manageable level for many
14 years.

15 Then he required medications. And then even
16 with medications, diet, and lifestyle changes, his
17 triglycerides continued to climb.

18 FCS puts an extra burden on the caregiver
19 and the family. I live with a daily fear that my
20 husband will have another episode of pancreatitis.
21 Our family meals revolve around what he can and
22 cannot eat. And social events and food pose an

1 area of stress for both of us.

2 More times than I can count, my husband has
3 come home from an evening out and ended up with an
4 episode of pancreatitis. No one wants to see their
5 spouse sick, so it's just easier to stay home.
6 That creates a sense of isolation for both of us.

7 As a critical care registered nurse, being a
8 witness to my husband in chronic pain and not
9 knowing how to help him has been a great source of
10 heartache for me. To see him go through those
11 repeated episodes of debilitating, excruciating
12 pain has created a sense of helplessness and
13 hopelessness in me. The fear of losing him is
14 there every day.

15 The effects of this disease has caused my
16 husband to need a lot of downtime. FCS is also
17 known to cause memory loss and an inability to
18 concentrate. These symptoms have had an impact on
19 his career. He has shown up late to work because
20 he couldn't leave home due to vomiting and
21 diarrhea. He's been hospitalized many times with
22 pancreatitis, thus missing work.

1 I've changed my work schedule as a
2 registered nurse to be home with him because I
3 feared to leave him alone. That left me with guilt
4 and fear when I did have to go to work.

5 My husband has been participating in a
6 clinical drug trial for the drug volanesorsen over
7 the last two years. Prior to his participation in
8 the clinical trial, he experienced fatigue on a
9 daily basis. He had frequent bouts of vomiting and
10 diarrhea many times a week. He experienced severe
11 abdominal pain several times a month.

12 Since the trial, my husband has had more
13 energy, no pain, no pancreatitis, no vomiting and
14 diarrhea. He's been a more active participant in
15 our family activities. He's no longer sitting on
16 the sidelines watching life go by.

17 He's happy and engaged and, because of that,
18 I am happy and hopeful for our future together.
19 This medication can be a source of hope and healing
20 for the individuals and their families suffering
21 from FCS.

22 Taking volanesorsen does require regular

1 monitoring, but the debilitating effects of this
2 disease occur on a daily basis. The regulations
3 for monitoring are on a regular basis. The
4 benefits would be felt on a daily basis. I think
5 daily benefit, regular monitoring says it all.

6 Thank you for your time today.

7 DR. WILSON: Thank you very much. Next
8 speaker is maybe two people. Speaker number 6,
9 please introduce yourself and any organizations you
10 represent.

11 MR. CHILDERS: My name is Mark Childers from
12 Palos Hills, Illinois, near Chicago. I was
13 diagnosed with FCS in 2016 by Dr. Michael Davidson
14 after having the genetic testing.

15 I'd been having symptoms since I was 40. My
16 first hospital stay was 8 days with a triglyceride
17 level of 14,000. What I want you guys to
18 understand is, before I had FCS, I had a normal
19 life. I took my kids out, we enjoyed life, we had
20 vacations, I coached travel baseball.

21 Through this journey, I've been hospitalized
22 over 100 times with pancreatitis. I was told I was

1 fat, so I lost 70 pounds. The episodes increased.
2 We followed an extreme low-fat diet and then my
3 wife, who is my savior, really, put us, as I also
4 developed diabetes -- so we were on a low-carb,
5 low-fat diet together.

6 It got worse. Took all the statins.
7 Nothing works. Concentrated insulin, nothing
8 works. So my new life now consists of one good day
9 out of the week would be me being able to get up
10 and do laundry. I have chronic pain every day.

11 They ask you on a scale of 1 to 10. I'm at
12 a 5 every day. We can't take family vacations. I
13 have to have my doctors' team notes in case I get
14 sick here in Maryland and I have to go to the
15 hospital.

16 I woke up this morning and didn't even know
17 if I was going to be able to make it. It affects
18 your mind. It's not just a financial thing. It's
19 not just a physical thing. I've went to my wife
20 and said, "I'll completely understand if you
21 divorce me because you did not sign on for this."

22 My children -- who wants to have their child

1 come to you 10 times a day, "Dad, are you okay, do
2 we need to take you to the hospital?"

3 I found out that there's a drug that can
4 help me. And that's why I'm here today, because
5 this is my last chance. I was told by my medical
6 team -- I have a medical team of a lipidologist,
7 endocrinologist, a GI -- and my GI doctor told me,
8 "We need to be taking your pancreas out now."

9 I said, "Can we just hold on a little bit
10 longer?" because I have spoken to people who have
11 been on the drug and, even though I have five
12 genetic mutations, I did not meet the criteria for
13 the trial. This is my last chance. I hope you
14 guys give it to me. Thank you.

15 DR. WILSON: Thank you very much. So our
16 next speaker is speaker number 7. Please introduce
17 yourself and any organization that's sponsoring
18 you.

19 MS. GOETZ: Sorry. Good afternoon. My name
20 is Melissa Goetz and I'm here today on my own to
21 speak about my experience with familial
22 chylomicronemia syndrome on behalf of the FCS

1 Foundation.

2 Five years ago, my 7-week-old daughter,
3 Giuliana, was genetically diagnosed with
4 lipoprotein lipase deficiency. After an episode of
5 acute pancreatitis, her triglycerides were over
6 24,000.

7 At that time, I was certain of two things.
8 One, I would never meet another individual with
9 this one-in-a-million disease. And two, I would
10 never in my lifetime or hers see an opportunity for
11 treatment.

12 Thankfully, I am now wrong on both counts.
13 Five years have passed and not only have I met
14 others with FCS, but I am the cofounder and
15 co-president of the FCS Foundation.

16 This position has allowed me to connect with
17 patients and learn the real day-to-day struggles
18 FCS has on them. The burden of disease extends far
19 beyond diet. Members of the FCS community
20 regularly report experiencing diarrhea, constant
21 abdominal pain, fatigue, social isolation, memory
22 loss, and of course the constant threat and reality

1 of pancreatitis, a result of high triglycerides
2 consistently above 800 and often reaching well over
3 10,000.

4 Individuals I have met with follow low-fat,
5 low-carb diets. They stay hydrated. They stay
6 active. They don't smoke. They don't drink.
7 They've met with specialists in endocrinology,
8 metabolism, lipidology, gastroenterology. They've
9 been on fibrates, omega 3s, and assorted cocktails
10 of other drugs in the hopes of managing and
11 reducing not just their triglycerides, but the day-
12 to-day pain they experience associated with FCS
13 with no success.

14 They have had unnecessary surgeries,
15 removing their spleen, gall bladder. They have
16 regular plasmapheresis and some have even been
17 advised of having local surgery. They have lost
18 their jobs, their homes, relationships. They have
19 given up on dreams of having children of their own.

20 They've dropped out of school or taken less
21 ideal jobs earning less than they would in order to
22 accommodate their health struggles.

1 As with any therapy, there are sure to be
2 side effects, PROs and cons, that must be
3 considered. A drug that can lower triglycerides
4 and offer day-to-day relief would outweigh the
5 negatives, especially when no other option exists.
6 A life without any option, the life that currently
7 exists for FCS patients, is not a life I want for
8 my daughter or anyone living with this disease.

9 I tell my three children they can grow up to
10 be, go, or do anything they want in this life. But
11 when I tell this to Giuliana [ph], the fear and
12 anxiety of the realities of FCS make me wonder if
13 I'm telling her the truth.

14 I thought about what a therapy for FCS would
15 mean for my daughter when she grows up and I ask
16 those in the FCS community what it would mean to
17 them. And here are some of their answers in their
18 own words, words that reflect our FCS patient
19 survey that was included in the foundation's
20 submission to the docket you received.

21 In their words, a treatment for FCS would
22 mean not living in fear anymore that every time my

1 husband starts having belly pain it is going to
2 turn into pancreatitis and he is not going to die
3 an early death.

4 It means that my teenage grandchildren can
5 live a more normal life, not living with constant
6 pain, not living in fear of pancreatitis.

7 It would mean that I would be a better mom
8 to my daughter. The daily pain, fatigue, constant
9 anxiety, and dietary restrictions play a big role
10 in my life and trying to push through it all so
11 that I can be the best mom for my daughter is my
12 greatest challenge.

13 It would mean that I could breathe. I could
14 finally release the internal breath I have been
15 holding for 20 years. It would mean that I could
16 get a good night's sleep. My son is now two years
17 old. However, he was hospitalized at 3 weeks old
18 with life-threatening organ failure.

19 I wake up every couple of hours to check on
20 him. I want some rest for my mind and my body.
21 Having a treatment would ease the anxiety and
22 burden of never knowing if today is the day I don't

1 leave the hospital.

2 I hope my story here today helps you to
3 understand the unmet need and burden of disease of
4 FCS and why volanesorsen is the crucial next step
5 in helping individuals living with FCS move forward
6 in their lives. Thank you.

7 DR. WILSON: Thank you very much. Next is
8 speaker number 8. Please introduce yourself and
9 any organization that's sponsoring you.

10 DR. DAVIDSON: Good afternoon. My name is
11 David Davidson. I'm here on my own today. As far
12 as COI, I was a site investigator for CS7 and did
13 attend one ad board.

14 Thank you for allowing me the time to speak
15 on behalf of my patients and others who deal with
16 this difficult condition, FCS. My name is David
17 Davidson. I am a lipidologist in the Chicago area
18 and I'm here on my own today to try to advocate for
19 volanesorsen to be an option to treat this
20 previously untreatable condition.

21 I know that you have and will be hearing
22 from several individual patients, stories, and

1 scientific data. I would like to add the
2 perspective of what it is like trying to care for
3 these patients and what it is like using
4 volanesorsen through my experience as a site
5 investigator.

6 Prior to this, I had 1 patient with FCS. He
7 had frequent episodes of pancreatitis, did not
8 respond to any therapy I gave him, and despite his
9 best efforts, the closest that diet could get to
10 controlling his triglycerides was to bring his
11 numbers down from greater than 4,425, which is the
12 upper limit that our lab will report, to just about
13 6 weeks ago, he was 1,790, still at very high risk
14 for another episode of pancreatitis.

15 His last hospitalization was less than 6
16 months ago and, clearly with his triglycerides
17 still hovering around 2,000, it's only a matter of
18 time before his next episode. The major problem
19 for him is that he won't even follow up with me
20 because I have nothing to offer him.

21 What's the point of coming to see me when
22 I'm just going to tell him that he needs to eat

1 differently? He has heard that several times
2 already. Why would this time yield different
3 results?

4 Since becoming an investigator, this
5 isolated incident became a much more common event
6 for me. I got referrals from several of the other
7 hospitals and systems in the area as well as
8 referrals from four outside states.

9 That's how little success anyone anywhere
10 has with treating this condition. Now, my patients
11 with FCS has gone from 1 who won't come to see me
12 anymore to about 8 who I am either the primary
13 physician or consulting for across multiple states,
14 including Mark, who you heard from, when he came to
15 see me to try to get enrolled in the trial.

16 We weren't able to, as you heard before. I
17 sent him straight from my office to the emergency
18 room because of an acute episode of pancreatitis.
19 Throughout my experience in the trial, I have seen
20 platelets drop. I monitor them closely and I
21 adjust the dosing as needed.

22 I'm happy to review the labs frequently

1 because I have seen my patients live without
2 pancreatitis and their quality of life improves
3 greatly when some of the daily symptoms and the
4 fear of pancreatitis can be removed.

5 I have never seen a group of patients so
6 eager to participate in a clinical trial for the
7 hope that some of these pains can be improved.
8 These patients are rare and the enhanced
9 surveillance is something that, in my experience,
10 physicians and patients are happy to adhere to
11 because the alternative is completely inadequate.

12 The challenges that the medication bring up
13 are nothing compared to the challenges that the
14 physicians and patients deal with on a daily basis.
15 Having an option, any option that can take away the
16 pain of pancreatitis, the fear of pancreatitis, the
17 daily abdominal discomfort, not to mention the
18 social, cognitive, and workforce issues that happen
19 when someone has FCS.

20 I'm advocating for the approval for
21 volanesorsen so that these rare and incredibly
22 difficult-to-treat patients have a single option to

1 try to improve their lives. Other difficult-to-use
2 medications have been approved for diseases with
3 similar frequencies in the population like
4 homozygous FH.

5 Even HoFH, which has very high mortality, I
6 would argue doesn't have nearly the kind of
7 morbidity associated with it that FCS does. FCS
8 patients have more frequent hospitalizations, have
9 difficulty holding down jobs, and have more
10 emotional and social dysfunction.

11 I would urge for approval of volanesorsen to
12 give us the practitioners and the patients
13 something to improve the treatment of this
14 devastating condition. Thank you for your time.

15 DR. WILSON: Thank you very much. Next,
16 we'll hear from speaker number 9. Please go to the
17 podium, introduce yourself and any organization
18 that's sponsoring you.

19 MR. TITLEBAUM: Good afternoon, everybody.
20 Thank you for the opportunity to address the EMDAC
21 open public hearing on this historic day for FCS
22 patients. My name is Joseph Titlebaum and I am the

1 chairman of the National Pancreas Foundation. I
2 live in Bethesda, Maryland.

3 The NPF is a national nonprofit that
4 provides hope for those suffering from pancreatitis
5 and pancreatic cancer through funding cutting-edge
6 research, advocating for new and better therapies
7 and providing support and education for patients,
8 caregivers, and healthcare professionals.

9 I became involved with the NPF because my
10 mother suffered from acute necrotizing pancreatitis
11 and my father suffered from pancreatic cancer. My
12 mother's fight with pancreatitis involved multiple
13 surgeries at the George Washington University
14 Hospital in Washington, D.C. and a 6-month extended
15 convalescence at my home while we had infants.

16 I'm here today to speak a little bit about
17 what it is to suffer from pancreatitis since the
18 majority of FCS patients ultimately also suffer
19 from pancreatitis. The NPF has no financial
20 interest in the success of the sponsor's
21 application, although Akcea has been a financial
22 supporter of the NPF.

1 Pancreatitis, as you know, is a debilitating
2 disease. It frequently triggers intense pain that
3 leads to extended periods of hospitalization,
4 preventing patients from eating regularly, working,
5 or leading normal lives.

6 While some chronic pancreatitis patients
7 have benefitted from new surgical endoscopic or
8 other treatments, many others simply manage with
9 regular hospital visits, pain medications, and
10 dietary supplements that aid in the digestion of
11 fatty foods.

12 Through my work with the NPF, I have gotten
13 to know many patients who have learned to manage
14 the terrible consequences of pancreatitis. Those
15 who have endured multiple surgeries include islet
16 cell transplants and others who are not candidates
17 for a surgical cure and are forced to find a way to
18 live with intense pain as a chronic condition.

19 I have learned to admire their courage in
20 the face of adversity, but I believe we can do more
21 to enable others to avoid this sort of debilitating
22 pain and the intense social stigma that is

1 associated with having pancreatitis.

2 If there is a treatment that could avoid
3 this sort of suffering among FCS patients, I think
4 the treatment should be made available for all
5 those who might benefit as quickly as possible. I
6 find it hard to imagine that the risks associated
7 with the new medicine exceed the costs and pain of
8 having to live with chronic pancreatitis.

9 On behalf of the patients in the United
10 States currently living with FCS, we urge you to
11 vote to approve volanesorsen. Thank you.

12 DR. WILSON: Thank you very much. Next,
13 we'll hear from speaker number 10. Please
14 introduce yourself and any organization that's
15 sponsoring you.

16 MS. SUTTON: Good afternoon. My name is
17 Lyndsey Sutton and I am here on my own to tell you
18 my story about living with familial chylomicronemia
19 syndrome. FCS, you make my life so hard almost
20 every single day. I cannot go an hour without
21 stressing that, because of you, I am going to get
22 pancreatitis.

1 I worry every single day about the symptoms
2 you may bring and what impact you are having on my
3 future health. The worst part is, I have grown so
4 accustomed to feeling so crummy every day that I
5 have forgotten that it isn't normal.

6 Even when I follow a strict low-fat diet,
7 you are still unhappy and make me suffer pain and
8 discomfort. You have succeeded in exhausting me.
9 You scare me more than anything because you hold my
10 health in your hands. I have been hospitalized
11 more than 30 times, one bout landing me in
12 intensive care for two weeks with triglycerides of
13 12,000.

14 My pancreas is 50 percent damaged from
15 necrotizing pancreatitis and the thought of ever
16 experiencing another bout is absolutely terrifying.
17 What you just heard was from a letter I wrote to
18 FCS two and a half years ago. This is a snapshot
19 of my life living with FCS before I received
20 volanesorsen.

21 I began taking volanesorsen over two years
22 ago. Since beginning this treatment, I have not

1 experienced a single episode of pancreatitis.
2 Volanesorsen has been life changing. Many might
3 think that not having pancreatitis is the best part
4 of all of this, but that's just one piece of the
5 puzzle.

6 My quality of life has vastly improved and I
7 wish that the study questionnaire had allowed for
8 me to better express this. My day-to-day symptoms
9 are gone and the constant fear and burden of
10 getting sick after every meal I eat is non-
11 existent.

12 Of course, I still follow a nearly fat-free
13 diet and avoid alcohol, but it is for those moments
14 that I am on vacation or out with friends to a
15 place where I have few dietary options that I am
16 free to live my life without the severe
17 consequences.

18 It is no secret that volanesorsen is not an
19 easy drug to take and I have suffered side effects.
20 I have dosed over 100 times and have experienced
21 two terrible injection site reactions where my
22 stomach swelled up, became very tender, and caused

1 me to vomit.

2 I would undergo this time and time again if
3 it meant that I would never have to experience
4 pancreatitis or daily discomfort. That is how
5 valuable this drug is to me.

6 A separate side effect that I have
7 encountered is a minor drop in my platelet count
8 and now I need to get routine blood testing every
9 two weeks for monitoring. But again, if this means
10 getting the drug, the risk is well worth it. My
11 life before this drug was hard.

12 Due to the rarity of this condition, most
13 people never experienced what I have experienced on
14 a day-to-day basis. My quality of life was much
15 lower than it should be for an adult my age. The
16 fear of getting sick lurked and was almost worse
17 than the actual case of pancreatitis because it
18 prevented me from partaking in activities that I
19 wanted to do.

20 Having said that, please know how life
21 changing and beneficial this drug is for me. You
22 know that, tomorrow, you are going to wake up and

1 be okay. Without this drug, I go to bed unsure if
2 I will make it through the night without a severe
3 case of pancreatitis.

4 Since being on drug, I do not question my
5 future health, I have energy, I feel healthy. As I
6 stand here today, after traveling 2,600 miles, I
7 hope my story resonates with you. I have lived
8 with FCS for 27 years and I am an expert.

9 Volanesorsen provides me with peace of mind
10 and hope. Though there are side effects, they're
11 minimal compared to the mental and physical pain I
12 have experienced without this drug. I want you to
13 know that I have been through unbelievable health
14 challenges and can say firsthand that this drug is
15 the best thing that's ever happened to me. Thank
16 you for your time.

17 DR. WILSON: Thank you very much. Our next
18 speaker is speaker number 11. Please introduce
19 yourself and any organization that's sponsoring
20 you.

21 MS. ALEXANDER: Good afternoon. My name is
22 Lori Alexander and I'm the director of the Lipid

1 Center of Excellence at the Jacksonville Center for
2 Clinical Research. I'm a clinical lipid specialist
3 and a registered dietitian/nutritionist.

4 I am here today speaking on behalf of the
5 Foundation of the National Lipid Association to
6 share our position that people living with rare
7 diseases such as FCS desperately need treatment
8 options. The NLA is a nonprofit organization of
9 physicians, nurses, registered dietitians, exercise
10 specialists, pharmacists dedicated to the signs of
11 lipidology.

12 The Foundation of the National Lipid
13 Association focuses on patient education, advocacy,
14 and support of those with lipid disorders,
15 including rare diseases such as FCS.

16 You've already heard quite a bit about the
17 impact of FCS, the hypertriglyceridemia due to the
18 lack of lipoprotein lipase and what these people
19 have gone through. These people live at constant
20 risk not only of severe pancreatitis, but all the
21 other daily symptoms that you've heard about, not
22 just physical symptoms, but all the cognitive and

1 emotional symptoms that go along with that.

2 This burden of illness really can
3 significantly affect not just their physical
4 issues, but also their career choices and many
5 other social activities that you've heard about.

6 Because of the types of mutations in these
7 people, many of the traditional lipid-lowering
8 medicines do not work. This is very devastating
9 for these people. Since they can't increase the
10 clearance of triglycerides with LPL enzyme, they
11 have to rely on increasing the production or
12 decreasing the production.

13 Of course, this is very, very difficult
14 because the only option they have is an extremely
15 ultra low or 0 fat diet. They also have to avoid
16 alcohol, limit severely simple carbohydrates and
17 sweets, and as you heard, this severely limits
18 their ability to enjoy life socially.

19 As a registered dietician/nutritionist, I
20 can certainly attest to the difficulty and
21 challenges these people experience in trying to
22 adhere to the only treatment, diet, that is

1 currently available to them and hoping that it
2 actually helps them.

3 People with FCS need to limit their daily
4 intake of fat to no more than 10 to 15 grams a day.
5 One tablespoon of olive oil has 14 grams of fat.
6 This makes it very challenging for them to meet
7 their essential fatty acid needs and they often
8 require special supplements such as medium chain
9 triglyceride fatty acids, which do not increase
10 triglycerides, simply in order to meet their
11 nutrient intake and to meet their calorie needs.

12 These can be very expensive and challenging
13 to incorporate into their daily diets, but focus on
14 diet alone is not enough. Many people with FCS, as
15 you've heard, continue to experience pancreatitis
16 and many of the severe symptoms, even when they're
17 following close to a 0-gram fat a-day diet.

18 The medication volanesorsen offers hope to
19 these people. Clinical trials as you've heard are
20 very encouraging, showing a reduction of 60 to 70
21 percent of triglycerides in these people, which is
22 huge as standard of care medications are

1 ineffective for them.

2 This is very exciting for these people, many
3 who have been struggling for years without adequate
4 medical therapy. Like many of you, I'm a scientist
5 and I can imagine if you try to put yourself in
6 their shoes. This treatment could greatly impact
7 the physical, emotional, and cognitive symptom
8 issues that they experience.

9 I greatly urge you to encourage it to pass.
10 Thank you.

11 DR. WILSON: Thank you very much. Next,
12 we're going to hear from speaker number 12. Please
13 introduce exactly what you're presenting because
14 we've already heard from you. Thank you.

15 MS. SUTTON: Hi, my name's Lyndsey Sutton
16 and I am speaking on behalf of Rebecca McFalls and
17 this is her exact testimony.

18 "Good afternoon. My name is Becky McFalls.
19 I haven't been reimbursed to be here today. I'm
20 here on behalf of myself as someone who lives with
21 FCS. I struggle with living with this rare disease
22 and I want to share my story.

1 I struggle with it day to day and it has an
2 impact on my dreams. I live every day not knowing
3 if or when my next pancreatic attack will be.
4 Regardless, I experienced pain, fatigue, xanthomas
5 from my feet to my shoulders. There are days when
6 I can't even do basic tasks that I should do;
7 laundry, dishes, grocery shopping.

8 That burden falls on my husband who is also
9 my caregiver. He also carries the burden of
10 working two jobs to meet our financial needs caused
11 by my disease.

12 Due to the frequent amount of hospital stays
13 and with him working two jobs, he can't be there
14 for me. It's hard on me. I'm fortunate, however.
15 My mom picks up that slack. Again, I feel like I'm
16 a burden.

17 But the burden of FCS on my family is more
18 than day-to-day suffering. It has an even more
19 profound impact. Growing up, I wanted a husband
20 and children. I met the man of my dreams, my
21 husband, Scott, but my dream of children didn't
22 happen.

1 My high triglycerides made pregnancy
2 dangerous for me for an unborn baby. I even gave
3 Scott the option to not get married so he might
4 have the opportunity for a family I couldn't give
5 him.

6 Scott didn't take me up on that thankfully.
7 He has been by my side for 10 years. The reason I
8 came here today is to ask you to approve this drug.
9 I'd like to try it. Low-fat, no-fat diet, exercise
10 programs, yoga haven't been enough to lower my
11 triglycerides.

12 This drug could mean less frequent ER visits
13 and fewer hospital stays. That would be wonderful.
14 It could be life changing. It could give Scott and
15 me the opportunity to be more financially stable
16 and healthier to be able to adopt a child.

17 It could give us a chance to travel and do
18 things we want to do as close to normal as
19 possible. I'd love to feel normal and not worry
20 about having a pancreatic attack away from home.
21 Please give Scott and me that chance. Thank you."

22 DR. WILSON: Thank you very much. Next,

1 we'll hear from speaker number 13. Please
2 introduce yourself and any organization that's
3 sponsoring you.

4 DR. ZANGENEH: Good afternoon. I'm Farhad
5 Zangeneh. I'm a clinical endocrinologist
6 practicing in northern Virginia. And I'm here to
7 represent AACE, American Association of Clinical
8 Endocrinologists. I used to be on the board of
9 directors. I'm a member of this association.

10 I'm making a statement on behalf of this
11 organization. AACE has received funding from many
12 pharmaceutical companies, including today's
13 sponsor. And AACE is the largest organization
14 representing clinical endocrinologists from 7,000
15 members, 97 countries, and mission of AAACE is to
16 enhance the lives of patients with endocrine
17 diseases and to help the clinical endocrinologists
18 with the latest state-of-the-art scientific
19 information.

20 Now, with that said, everything is a story.
21 So I have been actually here before for pio, lira,
22 degludec, and as of late, PCSK9 inhibitors. So

1 thank you so much for allowing, as a clinical
2 endocrinologist, to have access to those therapies
3 so I can help my patients.

4 Someone said, because I think these codes
5 are just so invaluable, a physician once said the
6 best medicine for humans is love. Someone asked,
7 what if it doesn't work. He said and smiled,
8 "Well, I'll just increase the dose."

9 I wish it was that easy. So I had sent some
10 slides in, but it was just late last night and I
11 missed the deadline. And of course, this story
12 began with the fact that I did not know this drug
13 existed. I didn't even know how to pronounce it.
14 I didn't even know how to pronounce the name of the
15 company.

16 To me, FCS was a slide on Cleveland Clinic
17 Board Review, which I am a co-director. I did not
18 even have a patient for many years, up until a
19 month ago, where Bobby walked into my office.

20 This is his story, so really, it's all about
21 the patient. So the interesting thing is, as I sat
22 here and listened to the stories here, all the

1 stories are very similar. 44-year-old Chinese
2 American, when he was a kid in kindergarten and had
3 GI issues, no one knew what was going on. It was
4 not until his mid-20s when he finished Marine Corps
5 that they diagnosed pancreatitis.

6 Forty-five total episodes to date, 25
7 hospitalizations; I mean, these are stats you don't
8 want to have. He gets married and his wife said,
9 "This is not a life to have. Let's get things
10 checked out." And basically, by the time they
11 evaluate him, he has splenomegaly.

12 The head of the pancreas are removed and, of
13 course, by this time, exocrine pancreas is
14 destroyed to some degree. Endocrine pancreas is
15 destroyed. They're in kind of a tailspin. He
16 loses a lot of weight in a reactive way, 160
17 pounds, goes to 130.

18 You have diabetes now, insulin requiring.
19 So he arrives in my office on insulin, so he has
20 become an acquired type 1 on basal insulin and
21 sliding scale, which are words endocrinologists do
22 not like to hear.

1 He has now acquired hypoglycemia, which is
2 pancreatitis on hypoglycemia, two of the greatest
3 side effects that can ever impact the human body,
4 the greatest equipment to ever walk the planet. So
5 when we talk about side effects, everything in life
6 is about risk-benefit ratio.

7 Anybody will cross the street and, of
8 course, if someone says I have to monitor for
9 platelets, and if you have to go to the hospital
10 every week, you're getting monitored all the time.

11 So I think the point is that we really have
12 to have a proportional response when we're dealing
13 with something like FCS, very rare, but very, very
14 impactful, so of course when he came to see me, his
15 triglycerides were in excess of 6,000, 6,700. So
16 on max niacin, 2 grams, max fenofibrate, max
17 prescription fish oil, I changed his insulin to
18 designer insulin. I got him carbohydrate counting.

19 He saw the best educator. He's got CGM.
20 He's almost near bionics. A1c is beautiful.
21 Triglycerides have dropped to 2,400. And as you
22 know, fasting triglycerides of 2,400, you're still

1 in pancreatitis country and of added statins,
2 window dressing, but still we are clearing 2,500
3 and no lower.

4 So again, that's the best that we can do.
5 So he's still having recurring episodes. So again,
6 I ask him to come today, but because of traffic, he
7 couldn't make it. We were going to share time.
8 And when I contacted AACE, I said, "Are you guys
9 going to this meeting?" They said, "Yes, we are."
10 I said, "Can I jump in?" And they said, "Yeah,
11 we'll give you the time," and I said, "Because I
12 have an actual live patient." This is actually a
13 very good scenario because really, after all, this
14 is about the patient.

15 I also want to thank my staff for staying
16 later this afternoon because I'm kind of the last
17 of a dying breed of NR1 clinical endocrinologists
18 that are still trying to make it here. So again,
19 if someone says this drug is expensive, of course
20 it will be, but it's not for everyone. It is for
21 someone who is on every medicine known to man.

22 Of course, lipoprotein lipase is under the

1 command of two hormones, hormone insulin, and
2 hormone thyroxine. Thyroid is normal and his
3 diabetes is perfect.

4 Then as I was driving, I said, "Well, you
5 missed coming in." He said, "Make sure they know
6 I'm not fat." He sends me his picture and he looks
7 like Bruce Lee. He is cut. He is built. Make
8 sure I'm not fat. So again, this is not exercise
9 and diet. And again, those are two words that
10 American College of Endocrinology does not like,
11 healthy eating and increased physical activity.

12 So this is, I mean, someone who's done the
13 very best he can. So I think the key here is, you
14 guys have access to things that you can protect by
15 doing extra safety. There is REMS. There is
16 additional testing.

17 So I think pretty much I know the mechanism
18 works on antisense. There is this thing called
19 common sense. And then there is this thing called
20 science. So I think, clearly, based on this
21 scenario that just dropped in my lap and the
22 patient, really, and hearing the suffering that

1 goes on here, our science is evolving to the fact
2 that we can help our patients correctly and deliver
3 a proportional response to the degree of suffering
4 based on physiology and biochemistry.

5 So thank you so much for your time.

6 **Clarifying Questions (continued)**

7 DR. WILSON: Thank you very much. The open
8 public hearing portion of this meeting has now
9 concluded and we will no longer take comments from
10 the audience.

11 Now, the committee will now turn its
12 attention to address the task at hand, the careful
13 consideration of the data before the committee as
14 well as the public comments. And I and the
15 committee really want to thank all of those who did
16 present and especially for some of you. We
17 recognize you are affected or you have family
18 members and you have personal stories.

19 We value that. That is part of this review
20 process. Some of you have not been to these
21 advisory committees before. We listen to you.
22 It's very important, what you contribute.

1 So the next is to finish with our questions
2 from this morning. And I have a list of names and
3 this was to follow up on, I believe, originally the
4 sponsor's initial presentation. And I am going to
5 go down the names.

6 Now, mind you, we have covered a lot of
7 material since then. We will then recycle back so,
8 when I read your name, if you can't remember your
9 exact question, you'll get another chance.

10 Dr. Epstein? Dr. Yanovski? I'm sorry.

11 Dr. Epstein, did you have a question from the
12 morning, from the sponsors?

13 DR. EPSTEIN: Yes. So in the CS6 protocol,
14 we saw the exclusion/inclusion criteria. I was
15 wondering why they didn't specify using the Atlanta
16 criteria for pancreatitis. As we know, a lot of
17 cases are pancreatitis or non-pancreatitis when we
18 look at them if they don't follow that criteria.
19 And that may have affected the robustness of the
20 study.

21 The other thing is, I didn't see
22 exclusionary for cholelithiasis,

1 choledocholithiasis, metabolic x syndrome,
2 bariatric surgery. I didn't see bariatric status.
3 There were a lot of things that were maybe not
4 included in your presentation.

5 I'm just wondering, were those things
6 actually in there, renal insufficiency, a non-
7 dialysis-dependent renal disease, et cetera. Were
8 they in the exclusionaries and how did you handle
9 those? Because that would have a definite impact
10 on your overall report.

11 DR. O'DEA: Thank you. To the first part,
12 let me start at the inclusion criteria. So yes.
13 Severe renal failure, severe hepatic disease were
14 exclusionary criteria. Recent surgery, not distant
15 surgery, such as you mentioned, were exclusionary
16 criteria.

17 In terms of where I was going to start,
18 which was the Atlanta criteria, we used the Atlanta
19 criteria in our trial. We used what is commonly
20 used in clinical trials, which is a modified form
21 of the Atlanta criteria. Audience I know that
22 Dr. Freedman can comment on that just to explain it

1 a little more if that's helpful.

2 But I think it probably is worth hearing
3 because it is the gold standard, as you say.

4 DR. FREEDMAN: That's a good point. So the
5 revised Atlanta criteria were used to adjudicate
6 all the events, both retrospective as well as
7 prospectively during the trial. And patients were
8 given either -- if you met the criteria exactly,
9 were definitive for acute pancreatitis versus
10 probable versus possible or otherwise other --

11 DR. O'DEA: Did we answer it?

12 DR. WILSON: Also I think, Dr. Epstein, the
13 question about the other exclusions --

14 DR. O'DEA: Yes. The other exclusions, I'm
15 not sure I have a list of them readily available.
16 But the top-line ones were severe
17 hypertriglyceridemia from other causes,
18 uncontrolled diabetes, i.e. hemoglobin A1c or
19 greater than 9, a patient on plasmapheresis if
20 plasmapheresis was an exclusion.

21 Active pancreatitis in the last number of
22 weeks and a prior history of, as I mentioned,

1 severe cardiac renal or hepatic disease. They were
2 the major exclusion criteria.

3 DR. WILSON: We didn't hear anything about
4 alcohol intake, either, presented.

5 DR. O'DEA: All of our patients were on diet
6 and of course diet alcohol is a core element of the
7 FCS diet. And so that was a critical part of the
8 dietary control of the patients, yes.

9 DR. WILSON: But were the patients excluded
10 who were alcoholic or had been drinking regularly
11 other than prior to the 6 weeks?

12 DR. O'DEA: Absolutely. These would be
13 patients with secondary causes of
14 hypertriglyceridemia. And just coming back to
15 where we started earlier this morning, for us it
16 was very important to define the population very
17 well, to look at the population with the highest
18 unmet need so that we would have the most
19 appropriate and optimal benefit.

20 That did include genetic testing, did
21 include LPL function as well as
22 hypertriglyceridemia. So we did try to narrow the

1 beam to those patients who were most in need of
2 treatment.

3 DR. WILSON: Can you explain how you got 750
4 and not 2,000?

5 DR. O'DEA: So 750 has been used before as a
6 cutoff for entry criteria for patients in these
7 hypertriglyceridemic trials. As was mentioned --
8 and I think it was Dr. Freedman, also -- 750 is
9 also where chylomicrons or Dr. Rader actually
10 predominate in the circulation.

11 So it really is the inflection point for the
12 appearance of chylomicrons in the serum. We did
13 mention that to the committee, we did measure
14 chylomicrons actually themselves for all patients
15 in the course of the trial. And they follow
16 exactly the same pattern of reduction as
17 hypertriglyceridemia themselves did.

18 DR. WILSON: Dr. Yanovski?

19 DR. YANOVSKI: My question was already
20 answered.

21 DR. WILSON: No questions. Dr. Ortel?

22 DR. ORTEL: I asked a question before about

1 the characteristics of the thrombocytopenia.

2 DR. WILSON: There was a question just
3 before lunch. Dr. Neaton?

4 DR. NEATON: I asked the question for them
5 to consider at lunch.

6 DR. WILSON: It's McCollister. Right? Yes.
7 Ms. McCollister?

8 MS. MCCOLLISTER-SLIPP: Hi there, a couple
9 of different questions. I'm not sure how to ask
10 that since I'm facing in the other direction. I
11 was curious about the connection or lack thereof,
12 apparent lack of connection between a decrease or
13 seeming therapeutic effect in terms of the drop in
14 triglycerides and a lack of change in abdominal
15 pain.

16 It looks like there's a little bit more
17 nuanced data in the briefing book that was given to
18 us ahead of time. But based on the slides that you
19 presented this morning, there doesn't seem to be
20 much of a decrease in pain and I was wondering if
21 you had any sense of why that might be the case.

22 Do we have any sense of sort of, in the

1 natural course of the disease, when pain starts to
2 become present? My hunch is, people probably are
3 not diagnosed prior to clinical symptoms or pain.

4 So that might not be a question that you can
5 answer at the moment, but I'm just wondering if
6 there's any sense of why that might be the case
7 because this is probably going to be an expensive
8 drug. It's going to be a difficult drug if it
9 doesn't have a reduction in pain and quality of
10 life and improvement in quality of life. Then I'm
11 just wondering about the benefits.

12 DR. O'DEA: So you're correct overall in our
13 trial and that may be a design issue on our part.
14 We did not collect clear evidence that pain overall
15 was positively impacted. We did collect evidence
16 that patients who came into the trial with pain at
17 the time they entered the trial had a reduction in
18 pain.

19 Now, we only collected the most severe
20 episode once per week, which was probably
21 insufficient data gathering for a population as we
22 just heard who have recurrent and chronic pain. So

1 that's the first thing.

2 The second thing is that we've actually gone
3 back in part of our development of a disease-
4 specific quality of life tool. We've gone back to
5 the patients who participated in the trial and,
6 among those patients we have asked those questions
7 about whether or not, again, similar to the
8 witnesses here, there was a subjective improvement
9 in pain and our evidence suggests that we have
10 subjective improvement in pain.

11 We did a statistical analysis on it. It is
12 statistically significant. And we are moving
13 forward, this quality of life tool, into full
14 validation at the present time.

15 MS. MCCOLLISTER-SLIPP: Second question is
16 related to the recommendations for your REMS
17 strategy. It seems like, as somebody who has to
18 get, based on FDA risk guidance, the insurance
19 companies tend to use that as gospel.

20 I take an expensive drug that requires
21 monitoring based on FDA guidance. Essentially,
22 insurance companies have a way of using that as a

1 block for people getting access to particularly
2 expensive drugs. Have you anticipated that
3 potential burden?

4 I mean, obviously, you want to make sure
5 that people are safe and that they don't have
6 severe side effects, but have you anticipated what
7 that potential burden may be? And have you looked
8 at or made any proposals for when that type of
9 monitoring can stop, that there may be less of a
10 need for that significant ongoing monitoring?

11 DR. O'DEA: So at the present time, we have
12 patients who have had more than three years of
13 treatment. We do not have a -- so let me just say,
14 in our REMS program, we plan to continue the
15 monitoring program that was shown this morning. We
16 will continue to assess the patients.

17 We will be running two different ways in
18 which we'll assess the patients. One is within the
19 REMS, through enhanced pharmacovigilance,
20 collecting information on events, but also through
21 our global registry study, which will be run in the
22 U.S. and other countries that we've been in, in our

1 clinical trials to collect more actively and
2 prospectively information that will help to guide
3 future advice to patients and physicians about the
4 appropriate monitoring frequency for the platelet
5 issue.

6 So at the moment, we don't have a new
7 guidance. As was said this morning, we're making
8 our guidance more conservative. Now, that doesn't
9 mean that necessarily at the present time we're
10 proposing more than every 2 weeks. And it's
11 important to point out two weeks is the initial.

12 It's only if you're normal that your
13 platelet count is measured every 2 weeks. If your
14 platelet count is not normal, you go to a higher
15 frequency of monitoring. But at the present time,
16 adding the weight element -- and I know there's
17 some controversy about whether that is fully
18 protective or not and we're open to that
19 consideration and discussion, but we do believe
20 it's an important addition to add to the monitoring
21 of patients.

22 MS. MCCOLLISTER-SLIPP: Then monitoring

1 presumably would require either going to the
2 doctor, going to a lab, getting your blood drawn,
3 waiting for the results.

4 DR. O'DEA: So in our trial, we've had home
5 care, as was said by one of the physicians who
6 stood up. And I think Dr. Baum has said the same
7 thing. Patients come from four states. So they're
8 not coming to their specialist's office. They're
9 having home care.

10 We have initiated an arrangement with one of
11 the big national labs, not so much that it will be
12 a central lab, but actually a central data
13 repository. We're more concerned about having a
14 data repository so that we have pathways to
15 communicate with the patient, and caregivers, and
16 multiple other stakeholders in the process.

17 So that is part of what we're going to do.
18 And to your earlier point, I'm not really on the
19 business side, although I carry a business card.
20 And we are concerned to facilitate as much as we
21 can for the patient, access to monitoring as well
22 as communication and protections through both the

1 REMS, all of the other patients' support processes
2 that we're putting in place, including potentially
3 some support in terms of testing that may be needed
4 to establish the diagnosis or any of the other
5 things that will facilitate access to care.

6 DR. WILSON: Dr. Sinclair, did you have a
7 question?

8 DR. SINCLAIR: In the ongoing open-label
9 extension trial, what are the projected dates for
10 the next analysis and the final analysis?

11 DR. O'DEA: So we have completed the
12 efficacy trial CS6 and it is in reporting at the
13 present time. CS7, which is the long-term 2
14 additional years of treatment, is no longer
15 recruiting as of the end of last year.

16 So since patients can be in that trial for 2
17 years, it will be close to 2 years before we have
18 the final report, but it's an open-label trial and,
19 for that reason, we're following the data very
20 closely. I get 12 e-mails a day with everybody's
21 platelet count, so we know exactly what everybody's
22 platelet counts are.

1 We know who's being notified of these counts
2 and we know what actions are taken. And we have
3 the opportunity to step in if we need to, if we
4 feel that the appropriate action is not being
5 taken.

6 DR. SINCLAIR: So the analysis would be, the
7 final analysis was projected?

8 DR. O'DEA: So it would be the end of 2019.

9 DR. SINCLAIR: There's no interim analysis
10 planned between now and then?

11 DR. O'DEA: No formal interim analysis, but
12 as I said, it's open label, so we're able to see
13 triglycerides. We're able to see platelet trends.
14 Yes.

15 DR. WILSON: I think we're now going to move
16 towards the questions that came up just before
17 lunch and start off with Dr. Kane. I apologize.
18 If you can remember your specific questions, we had
19 a whole series and then I close it, and then we'll
20 hear from the sponsor.

21 DR. KANE: Yes. You can guide me. I have
22 the questions that I left with you before lunch. I

1 do have additional questions both for the sponsor
2 and for the FDA. You just let me know when you're
3 ready for them.

4 DR. WILSON: So what we're going to do is
5 try to go as efficiently as possible for the
6 sponsor and then we're going to go to the FDA. And
7 then we're going to go into open discussion, so
8 that's our sequence from this time forward. Okay?

9 DR. KANE: I may use this, then, to lead
10 into the whole series of questions that I have. I
11 want to say, first of all, that I think the sponsor
12 needs to be acknowledged for the efforts extended
13 for this very rare condition to enroll and have
14 some 40 world sites. I think that's a pretty
15 enormous effort.

16 I do want to make a comment first also. In
17 the public session, I think this was very, very
18 informative, but it seems to me that the
19 experiences that we heard were not quite the same
20 experiences in the population that was studied in
21 the trial.

22 Now, I'm trying to understand that a little

1 bit better. One of my questions just before lunch
2 was the observation that I had both in some data
3 from CS6, CS7, and CS16. And it looked to me from
4 20,000 feet or so that the effect of an every-
5 other-week administration was, I'll say, similar to
6 the effect on triglycerides of every-week
7 administration.

8 I'm thinking with respect to both efficacy
9 and safety. So I wanted to ask the sponsor,
10 doesn't every other week get you close to where you
11 are with every week?

12 DR. O'DEA: So you are correct. And of
13 course, this is a post hoc, to be quite honest,
14 observation. And patients did segregate on a
15 weight basis. I think that's very important just
16 to remind everyone.

17 So for patients who are in the lower dose
18 because of the slightly lower body weight, on
19 average we have about a 60 percent benefit compared
20 to the 77 percent that you saw in the overall data.

21 So we do have about a 15 to 20 percent
22 difference between the 300 milligrams every 2 weeks

1 and 300 milligrams once a week. So one could argue
2 that 60 percent is an adequate benefit. In the
3 case of our initial treatment plan, we were looking
4 to optimize the benefit given the severity of this
5 disease.

6 As we heard, there were values of 10,000,
7 8,000, and 77 percent seemed like a better number
8 to target.

9 DR. KANE: Thank you. And if I can say
10 also, very brief answers will satisfy me very well.
11 Thank you. In your slide CO-47 to follow up with
12 this, then, you in your graph, showing the blue
13 completers, have dose reduced, but if I understood
14 it right, it wasn't a reductional dose. It was an
15 increase in the time interval.

16 DR. O'DEA: That's correct, every two weeks.

17 DR. KANE: That's fine. That's fine. And
18 may I continue, then, with my series?

19 DR. WILSON: How many more questions do you
20 have, just in the interests of moving forward?

21 DR. KANE: It's brief questions that have
22 brief answers. I want to be sure, first of all,

1 with the specific patients with FCS that have been
2 studied and described, I think we're talking about
3 56 unique patients as of the August report.

4 DR. O'DEA: So obviously, the FDA count the
5 numbers differently. We count 66. 1 patient did
6 not meet and that was, in retrospect, for technical
7 reasons either a qualification of genetics or --

8 DR. KANE: I was adding to gather the
9 patients who received drug treatment either in 6 or
10 7.

11 DR. O'DEA: Yes. You're correct. I'm
12 sorry.

13 DR. KANE: Now, the next point I wanted to
14 get to is that you have, I believe, in total 8
15 patients who had severe thrombocytopenia, platelets
16 below 50,000. And if I looked at the CS6 and CS7,
17 we had 6 in total below 50,000.

18 If I added the patients who received drug in
19 CS6 and the 43 who were de novo in CS7, we have
20 76 individuals and 6 of whom severe
21 thrombocytopenia. Is that correct?

22 DR. O'DEA: That's correct.

1 DR. KANE: The next thing I was looking at
2 then both in the graphs that the FDA
3 provided -- and I realize that there were varying
4 time intervals that were being applied to these
5 observations for these patients, but I think that
6 we do have some evidence that, for some, there was
7 a quite precipitous drop in the platelet count, and
8 then a variable recovery time after that.

9 So what I was trying to understand, then, if
10 you were measuring every 2 weeks a platelet count,
11 how sensitive would that be to detect a precipitous
12 drop. And I don't believe I understand that or
13 have a good enough view of that from the
14 information that we have here so far.

15 DR. O'DEA: So I do have a slide that I
16 think will cover all components of your question.

17 DR. KANE: I have a couple conceptual
18 questions that perhaps could be answered briefly if
19 you allow me.

20 DR. WILSON: If they're conceptual
21 questions, perhaps they could wait until we get
22 into joint FDA plus the sponsor. Let's try to get

1 through these, especially when we might need data
2 because then we don't have directed data questions.
3 Okay?

4 DR. KANE: Thank you.

5 DR. O'DEA: So in answer to your question,
6 we looked at the rate of decline from 100,000 down
7 to the lowest value measure for each individual
8 patient. We looked at the time to recovery to
9 140,000 and we looked at the time during which the
10 patient resided in that, sorry, high-risk low-
11 number range.

12 So if we look at the time that the patients
13 resided in that severe thrombocytopenia range, they
14 were between 3 days and 6 days. So that was the
15 period of time that they had values less than
16 50,000.

17 In terms of the way down, the range was 102
18 days to about 15 days, on the way down to 50,000.
19 And the recovery time to normal ranged from about 4
20 days up to about 40 days.

21 DR. WILSON: Can we move forward?

22 Dr. Ortel, did you have a question for data

1 clarifications?

2 DR. ORTEL: Yes. I had two questions. One
3 was focused on the quality of thrombocytopenia.
4 And by that, I mean, were other cell lines
5 affected, what do the red cells look like, was
6 there thrombocytopenia, what were the
7 characteristics of the thrombocytopenia.

8 That drives into the second question because
9 a number of these patients, it sounds like, when
10 they get to severe thrombocytopenia, they are
11 treated with other things, not just withdrawal of
12 the drug. They had listed they were getting
13 intravenous steroids, they were getting IVIg.

14 These are not necessarily benign treatments
15 and, if the hematologists to whom these people get
16 referred doesn't quite know what the mechanism of
17 the thrombocytopenia is, these patients may get
18 inappropriate treatments. And I was wondering how
19 were you going to try to educate the hematology
20 community about what to do with these.

21 DR. O'DEA: Yes. So if you don't mind, for
22 the first question, I'll ask Dr. Scott Henry to

1 respond as regards to work we've done on the other
2 cell lines and then also Dr. Sandy Shattil, who's
3 our consulting hematologist, who studied each one
4 of these patients, will comment on the use of
5 steroids.

6 It's an ITP protocol that we follow.

7 DR. SHATTIL: [Inaudible - off mic]
8 University of California at San Diego. With
9 respect to whether blood cell types were affected,
10 in the patients who developed platelet counts less
11 than 50,000, there was no change in white count.
12 There was no change in hemoglobin levels.

13 The peripheral blood smears that were
14 available by report did not show any red cell
15 fragmentation or spherocytosis. And in 2 patients
16 who had bone marrow histology examined, cellularity
17 was normal, including megakaryocytes. That's the
18 information we have on that.

19 With respect to the treatment, I share the
20 committee members' concern about potential
21 overtreatment of grade 3 thrombocytopenia in
22 particular. And in looking at the treatments these

1 patients received at the discretion of the
2 investigators, a short course of corticosteroids
3 was administered to some, but not all of these
4 patients.

5 One patient received IVIg and some patients
6 recovered with no specific treatment. The label
7 will include an indication that hematologist,
8 presumably an expert hematologist, will be
9 consulted when there is either grade 3 or grade 4
10 thrombocytopenia. Hopefully, overtreatment can be
11 avoided and specific necessary treatment
12 administered.

13 DR. WILSON: Are we resolved on that to move
14 forward? The next data in query was from me. It
15 was relevant to a slide by the sponsor, 58, and we
16 have an estimate of effectiveness for pancreatitis,
17 reducing the risk, and the question was, if there
18 was a trial, how many people would it take and for
19 how long, number of persons or number of person-
20 years of exposure to potentially show that this
21 molecule can reduce risk of pancreatitis?

22 DR. O'DEA: Dr. John Balser, our consultant,

1 statistician, will address that if you don't mind.

2 DR. BALSER: John Balser. I'm a biostat
3 consultant for Akcea. What I'd like to do actually
4 is address two questions at the same time if that's
5 all right because Dr. Neaton actually asked the
6 question about the enrichment for pancreatitis in
7 the study, CS6, and did we have an anticipated rate
8 of pancreatitis that we might have seen for the
9 placebo patients.

10 I think that's actually directly related to
11 this question and in fact is proper to position it
12 as a rate, not a frequency. As my statistical
13 colleague at the FDA pointed out, a frequency
14 analysis is not really appropriate if you've got a
15 different duration of observation.

16 So what I'd like to do is actually show you
17 the rates that we actually calculated, but first
18 let me address Dr. Neaton's concern and/or
19 question. We had anticipated approximately a rate
20 of .2 incidents per patient-year because that's
21 roughly what we see in the literature actually
22 between .2 and .35.

1 On that basis, we would have expected
2 somewhere between 5 and 8 placebo patients that
3 have had pancreatitis on this study. We didn't see
4 quite that many, but what I can show you is what we
5 actually did get.

6 That's going to be related to the question
7 of study design. So what you can see here is, we
8 did calculate the rate of pancreatitis events both
9 for volanesorsen and placebo patients. The bottom
10 two rows actually give what we believe would be the
11 proper rate, which is based on total duration of
12 observation, which was 29 patient-years for
13 volanesorsen and 31.8 patient-years of observation
14 for placebo.

15 But what you can see is the incidence rates
16 per patient-year of observation, .03 in
17 volanesorsen and .12 in the placebo group, on the
18 basis of this kind of information, it would require
19 a very, very large number of patients. As you
20 know, this is a very rare disease and pancreatitis
21 is a somewhat rare event historically.

22 So on the basis of this, we actually would

1 have calculated somewhere well in excess of 400
2 patients in a 1-year trial. We don't think that's
3 a feasible study to actually conduct. But again,
4 it is based on rate. It's not a frequency type
5 analysis.

6 DR. WILSON: Yes. Dr. Neaton?

7 DR. NEATON: Can I just follow up on this a
8 little bit? I mean, this relates in my mind to
9 some of the other discussion around the whole
10 target population that you're seeking an indication
11 for.

12 DR. BALSER: Sure.

13 DR. NEATON: It's because the indication
14 that we saw earlier today was very broad and didn't
15 include anything about the history of pancreatitis.
16 And so if you put the slide back up that you just
17 showed, that's a starter.

18 So presumably, what you're doing here is,
19 you're counting person-years of risk irrespective
20 of taking treatment.

21 DR. BALSER: I'm sorry. I don't know what
22 you mean by irrespective of treatment. We've got

1 two columns.

2 DR. NEATON: I'm looking at the next-to-last
3 row, the total duration of follow-up.

4 DR. BALSER: Yes.

5 DR. NEATON: So basically, what the FDA
6 statistician pointed out appropriately, is that the
7 odds ratio of .31 was likely way overestimating the
8 potential benefit because the duration of treatment
9 was different for the study drug compared to
10 placebo.

11 So as I recall, his rates, the rate ratio,
12 would have been something like .82 compared to your
13 odds ratio of .31. And so I don't understand the
14 duration of observation here because that must
15 imply you're discounting all person-years of
16 observation irrespective of whether the person was
17 taking treatment. Is that true?

18 DR. BALSER: I think you can actually see
19 both because the two rows above that actually are
20 normalized or adjustment for duration of treatment.
21 In fact, the proper analysis into some ITT analysis
22 would be based on patient-years of observation.

1 DR. NEATON: Yes. If you were following
2 actively and appropriately everybody for
3 pancreatitis, that's true. And that's another
4 question we'll come back to, but even the row above
5 that, I believe, perhaps we could ask the FDA
6 statistician to comment, get this straight for us,
7 is different.

8 DR. BALSER: Yes, sorry. I do need to point
9 out that this observation does include observation
10 for incidence of pancreatitis. Patients were
11 followed. In fact, there's only 2 patients out of
12 the entire set of volanesorsen patients who have
13 less than 24 weeks of observation follow-up for
14 pancreatitis.

15 DR. WILSON: So also here, have you made
16 these calculations for persons who have already
17 experienced at least one episode of pancreatitis in
18 the trial?

19 DR. BALSER: Yes.

20 DR. WILSON: Yes, because this is all-comers
21 versus 33 and 33, but there's a smaller number who
22 have a higher risk because they've already

1 experienced one episode of pancreatitis prior to
2 ever being in the studies.

3 DR. NEATON: Maybe we can put up slide 51 in
4 your presentation. I mean, the rate's on here, but
5 I guess I was surprised -- these are very small
6 numbers -- not to comment on the subgroup analysis
7 per se, but kind of from the discussion that
8 motivated this trial in the study as well as the
9 public hearing, there were only 11 people in this
10 study that had more than 1 event in the past 5
11 years?

12 DR. O'DEA: That's correct, but 78 percent
13 of the patients had an attack of pancreatitis at
14 some point.

15 DR. NEATON: So you excluded apparently then
16 large numbers of people with this condition with
17 chronic pancreatitis. Is that true?

18 DR. O'DEA: No. I'm not sure how one makes
19 that --

20 DR. NEATON: I just don't understand why
21 these numbers are so low, why 11 out of 66 with
22 only more than 1 event in 5 years. It just seems

1 like the target population here is not enriched
2 like you thought it was.

3 DR. O'DEA: So this is a population in a
4 trial who were very well curated, who were being
5 followed very closely, and who were adhering to
6 diet. So one might expect the rate to be slightly
7 lower than you might find in the open community.

8 So there's only one natural history studied
9 and it looks prospectively at the rate of
10 pancreatitis in this population. And they come up
11 with a number of 1 attack every 4 to 5 years on
12 average for a patient.

13 DR. WILSON: Yes. Dr. Epstein, you had a
14 point to make?

15 DR. EPSTEIN: Yes, two points about that.
16 One, these patients in the placebo; did they meet
17 the Atlanta criteria strictly for pancreatitis or
18 were these just people who were told they had --

19 DR. O'DEA: These were curated. Sorry. All
20 of these, the retrospective, the 5-year look back,
21 and the on-study were all curated by the same
22 independent committee against the Atlantic

1 criteria.

2 DR. EPSTEIN: To Dr. Neaton's point, with
3 this being a different population than what we're
4 hearing from these folks over here, did you study
5 the xanthelasma, the retinal changes? We didn't
6 hear anything about what's happening to their
7 overall condition.

8 You've got some of these patients on it for
9 a year. We'd expect to see regression of those
10 secondary signs and symptoms. We didn't hear
11 anything about that and it just makes you wonder.

12 DR. O'DEA: Right. There was only 1 patient
13 with active xanthomata at the time they entered the
14 trial. About 25 percent of the patients had had
15 xanthomata, but the majority of patients had not
16 had xanthomata in the past. We did do serial
17 fundoscopic examinations in the population.

18 We did not have enough data because lipemia
19 retinalis was not seen in enough patients for us to
20 be able to deduce that we had an effect, but we did
21 have the effect on serum triglycerides and, at the
22 end of the day, the most important thing for the

1 patients, I think, as we've heard, is the avoidance
2 of risk by reduction of triglycerides.

3 So I think we're able to deliver a
4 substantial reduction in risk to the population and
5 we do think that these data on triglycerides; CS16
6 without any filtering of the data -- we showed a
7 statistical reduction. Now, it was not a pre-
8 specified analysis, but it was statistically
9 positive.

10 In this look back analysis, in those at
11 highest risk, we did see a statistical benefit and
12 overall, in the CS6 population, we had 4 events in
13 placebo and 1 event on active treatment at a very
14 different triglyceride level.

15 So we do believe that there's certainly at
16 least a numeric if not a significant impact on
17 pancreatitis. And I think, as we've heard from
18 patients today, they've had a period of
19 pancreatitis re-existence while on treatment.

20 DR. WILSON: Dr. Smith from the FDA, you
21 wanted to make a comment?

22 DR. SMITH: I'd like to walk back a bit to

1 Dr. Ortel's question. He was raising a question
2 about mechanism of the platelet reduction and the
3 appropriateness or potential inappropriateness of
4 therapy with steroids or IVIg. And I was wondering
5 if you could clarify maybe for us in the committee
6 what your current recommendations are in your open-
7 label trial regarding steroid use in patients who
8 develop platelet counts less than 50,000.

9 DR. O'DEA: So our current practice is the
10 same as our proposed label, which is any patient
11 who reaches a value of 25,000 or lower should be
12 treated with steroids. And any patient who reaches
13 25,000 or lower should also have a hematology
14 consult on recovery to ensure that there's no
15 secondary reason why this may have occurred.

16 DR. SMITH: Right. So the hematology
17 consultation was mentioned, but to Dr. Ortel's
18 point, your current recommendation is for the use
19 of steroids in patients with very low platelet
20 counts. Correct?

21 DR. O'DEA: That's right.

22 DR. WILSON: We have one more comment, I

1 believe. Dr. Cuaresma? I apologize for
2 mispronouncing your name.

3 MS. CUARESMA: It's okay. You can continue
4 calling me doctor as well even though I'm not.

5 DR. WILSON: I apologize for that, too.

6 MS. CUARESMA: Thank you.

7 DR. WILSON: It's honorific today. What can
8 I say? But please go ahead. You had a comment and
9 a clarification you wanted. Thank you.

10 MS. CUARESMA: Yes. The FDA slide had said
11 that a single dose at 300 milligrams injection
12 lasts 24h ours. So I guess the question is, if the
13 life or half-life is less than a day, I guess I
14 just don't understand why the injections are every
15 week or every other week and how that effects the
16 chylomicrons' breakdown until the next dose.

17 DR. O'DEA: Right.

18 DR. REN: I can answer this question because
19 it's from my slides. So go to my slide number 3.
20 So let me rephrase the question. The question here
21 is saying there could be a paradox, which the drug
22 concentration in the blood is pretty much all gone

1 at the end of the dosing day.

2 How can the triglyceride reduction effect be
3 kept for one week? Because the dosing regimen's
4 once a week. So the answer is that I just need to
5 show the table.

6 DR. WILSON: Keep advancing.

7 DR. REN: Yes. So where did drug go? It
8 disappeared from the blood and it's not excreted
9 from human blood. It's accumulated in the
10 peripheral tissue, such as in the liver, such as in
11 the bone marrow here, and in some other tissues.

12 The drug target is apoC-III mRNA. And which
13 organ is responsible for producing apoC-III? It's
14 the liver. So the drug is in the liver, highly
15 accumulated. And even if the blood concentration
16 is gone, you still have a lot of drug in the liver,
17 still doing its job.

18 MS. CUARESMA: Thank you. I have another
19 timeline question that kind of ties in with that.

20 DR. WILSON: Go ahead.

21 MS. CUARESMA: Thank you. So the other
22 question again has to do with timeline with

1 triglycerides. It shows it at 77 percent of the 3-
2 month mark and then at 55 percent at the 6 and then
3 I think down to 44 percent at the 12-month mark.
4 Why is there such a discrepancy and why are those
5 percentages -- is the body resisting it at that
6 point, at 12 months?

7 So although it says 77 percent reduction, it
8 looks like, over time, that's half of that in a
9 year. Does that make sense?

10 DR. O'DEA: So it does. It does. So what
11 we're looking at is, we're looking at the
12 compounding effect of some patients staying on the
13 same dose, some patients having a reduced dose
14 through a change in the frequency of
15 administration, and some patients discontinuing
16 treatment.

17 So when all of those are put together,
18 there's a reduction in efficacy. But if you stay
19 on one dose, whatever that is, whether it's weekly
20 or biweekly, you have the same persistent
21 triglyceride value. So it's still 70 plus percent
22 at the full dose and it's 63 percent or so at the

1 half dose.

2 MS. CUARESMA: Thank you.

3 DR. WILSON: We have a few more questions.
4 Dr. Weber, you're up.

5 DR. WEBER: Thank you. For the sponsor,
6 just before I ask the question, I'm trying to get
7 my mind around the pancreatitis rate in the trial
8 and reconcile some of the observations that we had
9 from the higher study subjects in the public
10 hearing.

11 First question, do all the subjects, prior
12 subjects in trial know their study assignment at
13 this time?

14 DR. O'DEA: They do.

15 DR. WEBER: I guess the question I had was,
16 in terms of the rate of pancreatitis per patient-
17 year, do you have data on the rate before the trial
18 for placebo versus the trial and whether or not
19 there was a significant reduction in the rate of
20 pancreatitis such that there was a study effect
21 that was independent of the drug?

22 DR. O'DEA: So we do have that. That is

1 reported in our overall data. I don't believe I
2 have already made a slide with that. The analyses
3 we did were in the higher group, those who had more
4 than 1 attack, because 1 attack over the 5 years is
5 an expectation. More than 1 attack is not an
6 expectation and that's why we did the analysis on
7 that group.

8 We had, I think, 17 attacks in 4 patients in
9 that period of time. Overall, perhaps, I don't
10 know if we have such a slide. But I can provide
11 you with that information a little later. But let
12 me see if I have it.

13 DR. WEBER: Sure. I 'm just trying to
14 clarify if there was a study effect that's
15 confounding some of what we're seeing with regards
16 to the --

17 DR. O'DEA: I understand. Understand.

18 DR. KANE: Could I follow up with Dr. Webb's
19 question just to clarify further?

20 DR. WILSON: Please identify yourself.

21 DR. KANE: Robert Kane. Dr. Webb's concern
22 was the post-study knowledge of this treatment

1 augmentation. But I think we should recognize that
2 my reading of this; the majority of patients, some
3 80 percent, who had injection site reactions would
4 know what their treatment was on study. Thank you.

5 DR. WILSON: We also had a comment from
6 Dr. Low Wang.

7 DR. LOW WANG: So I have a question for the
8 sponsor and a question for the FDA. And so the
9 question for the sponsor is just going back to the
10 rationale for not testing this drug in pediatric
11 population, just thinking about the fact that when
12 patients develop pancreatitis for the first time,
13 we think that they have a higher risk for
14 developing pancreatitis down the line.

15 So the utility of using this drug in adult
16 population versus pediatric population is the horse
17 out of the barn already. I think, from the open
18 public hearing, it sounds like there are still a
19 lot of repeated episodes seen in the adults, but
20 could we prevent that by using this drug in
21 pediatrics. Well, let me stop there.

22 DR. O'DEA: So we do have a plan for

1 pediatric development of the drug, of course. As
2 was mentioned, it may take a long time for patients
3 to be diagnosed. That's not necessarily true in
4 every country. There are countries where there are
5 concentrations of patients and they're diagnosed at
6 a very early age.

7 I think we heard somebody was diagnosed in
8 their first few years of life and that's not
9 uncommon. Nursing children can be diagnosed with
10 this disease as a consequence of mother's milk.

11 So it can be diagnosed at every age. We do
12 have an active plan, as I say. We are initiating
13 our trial around the world in the same countries
14 likely that we are currently involved in and we
15 will have a solution for the pediatric population.

16 We have a different dose paradigm in terms
17 of scaling. We have learned and we do include our
18 learnings into our subsequent studies.

19 DR. LOW WANG: Actually, if I could just --

20 DR. WILSON: Do you have a follow-up? Go
21 ahead.

22 DR. LOW WANG: It's slightly different, for

1 the FDA. So this is for Dr. Roberts and this is in
2 the clinical review, slide 35. Now, this was a
3 slide that showed the platelet count of patients
4 who had episodes of epistaxis and petechiae.

5 So what I was wondering; these are the
6 platelet counts at the time of those events, but is
7 there any analysis of what happened to those
8 platelet counts later. Like, did any of those
9 patients experience later drops in platelet counts
10 after those events? Do we know that?

11 DR. ROBERTS: I don't think that we have an
12 analysis of what the platelet counts did after
13 these events. These were the previous platelet
14 counts right before the bleeding event. And I
15 don't believe we have one for what those platelet
16 counts did afterwards, although we do have patients
17 that did have very low platelet counts, like 8,000
18 that did have epistaxis and petechiae, but I don't
19 have a slide that shows that.

20 DR. SMITH: This is Jim Smith. We did look.
21 And it just made too busy of a figure, so I don't
22 think we actually have it to show the committee.

1 We looked at the platelet count immediately before
2 those events as well as the next platelet count
3 immediately after those events to get a sense for
4 whether or not the event could have been a
5 premonitory sign of a precipitous drop.

6 As I recall, in really none of the cases did
7 we have a precipitous fall after that particular
8 event.

9 DR. WILSON: So to follow up, Dr. Smith, the
10 point was, were individuals who had a bleeding
11 event or had the very low platelet count. It
12 seemed to me, from what we've seen so far, they
13 were on a trajectory to go low and then they still
14 got another dose. Is that fair to say?

15 I guess I'm sort of following up on the
16 earlier question. Can you predict that they're
17 headed low and they're going lower? Is that fair
18 to say or no?

19 DR. ROBERTS: I think it's difficult to
20 predict. I mean, there are examples where they had
21 12 doses and they were below 50,000.

22 DR. WILSON: So that does not resolve it.

1 So the next part; let me tell you the rest of the
2 afternoon. We'd like to finish on time. We have
3 lots of discussion questions. We have not followed
4 up with the FDA presentation from this morning.

5 What we'd like to do is to move to the FDA
6 clarifications as the next step, but go through
7 that rather quickly for any clarifications, so we
8 can move into our discussion.

9 The discussion will still be able to involve
10 the sponsor and FDA, but are there any pressing
11 clarifications from the FDA, especially related to
12 things? We'd like to have everything pretty much
13 on the table when we get to discussion. So yes.
14 Go ahead, Dr. Kane.

15 DR. KANE: Thank you. Kane. With regard
16 to the REMS proposal, I wanted to understand, is
17 there an experience to date with another REMS that
18 has some of these characteristics such as every-
19 they want-week blood counts, 1-month dispensing of
20 drug supply each month to the patient, and the
21 consistency of getting reports every 90 days with
22 regard to the treatment experience? Thank you.

1 DR. LaCIVITA: So there is some experience
2 with these different elements. They're not exactly
3 the same REMS. There are some REMS that are
4 comprised of some of these elements, so there is a
5 REMS that's currently approved with a 90-day status
6 form and that is more event driven to find out if
7 certain events were occurring and if monitoring was
8 occurring.

9 There are REMS that are approved that
10 require a lab value prior to dispensing the drug
11 and the 30 days is something that the sponsor has
12 proposed. We haven't discussed that within the
13 agency and it's more than likely related to a month
14 worth of insurance coverage. Does that answer your
15 question?

16 DR. WILSON: Dr. Morrato?

17 DR. MORRATO: Elaine Morrato, a question for
18 Dr. Roberts, clarifying on her slide 29, looking at
19 the platelet counts over time.

20 DR. WILSON: Which presentation,
21 Dr. Morrato?

22 DR. MORRATO: Her safety one, the clinical

1 review, Roberts's clinical review. It would help
2 this one. It says 29 on it.

3 DR. WILSON: Number 29 is the one with the
4 red dot. There it is.

5 DR. MORRATO: I thought this was very
6 interesting and I'm trying to reconcile it with, I
7 think it is, the equivalent of the slide from the
8 sponsor 66, which Dr. Budnitz kind of was also
9 asking about.

10 The sponsor's looks like the mean over time
11 is over 150. You're reporting a median of 122.
12 Can you just help me understand how are these
13 different if both of them are looking at platelet
14 counts over time? These seem to be dropping a lot
15 more than what we saw in the sponsor's mean counts.

16 DR. ROBERTS: I mean these are all of the
17 platelet counts, both planned and unplanned, so I'm
18 not clear on if that is the difference or not
19 between the two. And this figure would include
20 patients that are on drug and off drug as well. So
21 there's differential time on drug here, so that
22 someone may have gone off treatment.

1 There's two very low clusters of patients.
2 Their follow-up platelet counts after that are not
3 on treatment and I don't know if that's maybe from
4 the --

5 DR. MORRATO: Was incorporated into the
6 sponsor's slide, but all of that data would be in
7 your slide.

8 DR. ROBERTS: Yes.

9 DR. MORRATO: Very good; then one just
10 general question that might be helpful, since I
11 know the discussion we're going to have to do to
12 weigh two different life-threatening events. And
13 you see these kinds of things looking across drugs
14 at the agency. Can you help ground us with maybe
15 the best estimates of the clinical consequences of
16 these events?

17 So we saw some reports in the briefing
18 documents about mortality or hospitalizations
19 associated with pancreatitis. And what would it be
20 for drug-induced thrombocytopenia? Are they
21 comparable rates of mortality?

22 DR. ROBERTS: I would maybe refer to my

1 hematologist.

2 DR. DE CLARO: My name is Angelo de Claro.
3 I am the acting deputy director of the Division of
4 Hematology Products. We were consulted to comment
5 on what would be the risks for bleeding in this
6 case. It's very difficult to make that assessment,
7 given the small safety database, and traditionally
8 and without clearly understanding the mechanism, I
9 think it's difficult to really state what would be
10 the risk of bleeding, given the degree of
11 thrombocytopenia that was observed.

12 DR. MORRATO: Right. In general, everyone
13 is expressing concern over the risk. I'm just
14 trying to get a sense of what's the likelihood of a
15 really bad outcome when we say life threatening.
16 Is it 1 in 100 of these cases? Is it 1 in 1,000?
17 Is it rarer, more common? How do we in general for
18 other drugs?

19 DR. DE CLARO: It varies from drug to drug
20 and also concomitant medications. I know perhaps,
21 Dr. Ortel, would you surmise a range in this case?

22 DR. ORTEL: Yes. It is very difficult to do

1 that, but you can argue, from other kinds of
2 thrombocytopenias, let's say it's only the platelet
3 count that's low. There's nothing else wrong.
4 Usually, you don't have to treat a patient until
5 they get below 30,000.

6 The risk of spontaneous bleeding does not
7 really begin to go up until you get below 10,000.
8 That's why I'm very concerned about the
9 recommendation to give steroids for
10 thrombocytopenia without necessarily getting a
11 hematologist involved because it may not be
12 indicated at all.

13 DR. MORRATO: What's the mortality risk? I
14 mean, does everyone recover?

15 DR. DE CLARO: You can bleed anywhere and it
16 can be fatal.

17 DR. MORRATO: Right.

18 DR. DE CLARO: You could bleed in your head.

19 DR. MORRATO: Right. But is it very rare?

20 DR. DE CLARO: Once you get below 10,000,
21 the risk begins to go up. Once you approach 1,
22 those patients actually --

1 DR. MORRATO: So is it 1:1? Like, once you
2 get below that, you're 50 percent chance of death,
3 100?

4 DR. DE CLARO: I don't think that we have
5 enough data that I can tell you exactly a
6 percentage on that, but it is high enough that,
7 once you get below 10, you do have to initiate some
8 kind of treatment.

9 DR. MORRATO: Yes. But the reason I'm
10 asking -- and there may be more for
11 discussion -- is I worked on drug development that
12 had severe agranular cytolysis. And we had a lot of
13 discussion around what does the seriousness mean
14 and the consequence in today's modern medicine.

15 Maybe the death risk is much, much lower
16 than earlier data reported decades ago and I'm just
17 trying to get an anchor point with this because
18 we're having to compare and trade off, so thank
19 you.

20 DR. WILSON: So Dr. Shamburek, you had a
21 follow-up?

22 DR. SHAMBUREK: Somewhere in my notes, I

1 have that when you looked at actually the bleeding
2 AEs, most of them occurred with platelet counts
3 greater than 75,000 and it was suggested that this
4 suggests a platelet function rather than the
5 number, which kind of makes the number a hard thing
6 to deal with.

7 DR. WILSON: So Peter Wilson here. Also as
8 a follow-up, I was wondering about other
9 medications that patients may have dropped in on
10 that can cause thrombocytopenia. And some of the
11 most common are acetaminophen, NSAIDs, and aspirin,
12 which we've not heard about at all today.

13 Presumably, that would be part of a REMS,
14 but is there any data up until now even for those
15 drop-ins or medications that may have affected the
16 metabolism of the drug itself, actually what was
17 administered? Yes, Dr. Ortel?

18 DR. ORTEL: So I was going to follow up on
19 that. The one person did comment on animal data
20 that qualitative platelet defects were not seen.
21 And I don't know what they've got in humans as far
22 as whether or not there are any qualitative defects

1 on top of that.

2 Obviously, if you're taking aspirin, if
3 you're taking NSAIDs, and things like that, you can
4 have a qualitative platelet defect on top of that
5 which can modify that risk of bleeding.

6 DR. WILSON: Thanks very much. Dr. Neaton,
7 did you have one other question?

8 DR. NEATON: I had a two questions for the
9 FDA. One, I just want to say I thought Dr. Cambon
10 did a nice job of addressing a concern that I had
11 this morning about the counts that were showed
12 about pancreatitis.

13 Slides 50, for example, and 51 showed the
14 counts on treatment. And so he did an analysis
15 which took into account the time on treatment,
16 which is very different for the two groups, and
17 showed that they're much more similar. The rates
18 from his presentation were .11 and .09.

19 So then Dr. Roberts talked about adverse
20 events and I just wanted to ask her, if you apply
21 the same thinking to the adverse event summarize
22 that you showed, is it a fair assessment that we're

1 probably underestimating the difference in adverse
2 event rates between the active treatment group and
3 placebo group here?

4 I mean, actually, Dr. Ren made a comment
5 that I think is valid just when it comes to the
6 median kind of platelet levels. The more often the
7 nadir platelet levels, the more often you measure
8 platelets, the more likely it is you're going to
9 find a low one or a high one.

10 It's going to influence a lot of the
11 analyses, the differential follow-up in my mind.

12 DR. ROBERTS: Yes. I mean, I think that it
13 could. We did look at all of the adverse events
14 whether they were on treatment or not, so from the
15 beginning of the study all the way to the end of
16 the study.

17 But you're right. If you did discontinue
18 and you weren't being followed up for adverse
19 events, then yes, you might have be missing adverse
20 events.

21 DR. NEATON: Not only missing the numerator,
22 which I'm still a bit concerned about, it's

1 basically the denominator.

2 DR. ROBERTS: Right.

3 DR. NEATON: Because the analyses that were
4 shown on adverse events were largely adverse events
5 while people were taking therapy and so that was a
6 shorter period of time for the active drug versus
7 placebo.

8 DR. WILSON: So what we're going to do
9 next --

10 DR. NEWMAN: Can I ask another question?

11 DR. WILSON: Do you have another follow-up
12 on that?

13 DR. NEWMAN: I have a clarifying.

14 DR. BUDNITZ: Dan Budnitz. Just to follow
15 up on Dr. Neaton's point, I think the thing that's
16 so critical about this point is that, because the
17 dropout rate was so high and we don't have to think
18 about this in most studies, with a dropout rate
19 much lower, but I think halfway through the pivotal
20 trial, I think I saw that a quarter of patients
21 were no longer on study therapy, so for half the
22 trial, a quarter of the patients were not on

1 therapy.

2 So it changes. Maybe you want incidence
3 density for these kind of adverse event rates.

4 DR. WILSON: Dr. Sinclair, I'm sorry. No?
5 Dr. Newman, I apologize. You had your hand raised.

6 DR. NEWMAN: It's me. I have a question for
7 Dr. Roberts. It was mentioned in the briefing
8 document that, with other antisense
9 oligonucleotides, there was a cerebral bleed in a
10 patient. How should that influence our thinking
11 about this product?

12 DR. ROBERTS: I think it just highlights the
13 risk associated with thrombocytopenia. So that is
14 something that we consider when we see these low
15 platelet counts that we haven't seen a serious
16 clinical bleeding event. But as was said earlier,
17 when you have very low platelet counts, your risk
18 goes up for having a major clinical bleed.

19 DR. KANE: May I just clarify? I think you
20 just used the wrong word there. We haven't seen
21 serious adverse event. We haven't seen major
22 bleeding, but we've seen serious adverse events.

1 DR. ROBERTS: Correct, sorry, thank you.

2 **Questions to the Committee and Discussion**

3 DR. WILSON: I think are we pretty much
4 done? We can come back for more clarifications
5 with FDA or the sponsor, but we do need to get our
6 work done, which is open discussion. And so we're
7 now going to proceed to the questions of the
8 committee and the panel discussions.

9 I'd like to remind public observers that,
10 while this meeting is open for public observation,
11 the public attendees may not participate except at
12 the specific request of the panel. So first, we're
13 going to, I believe, pull up question, discussion
14 number 1, and I'm going to read this.

15 Partly, it needs to go into the record for
16 the recording. A reduction in fasting
17 triglycerides has been accepted by FDA as an
18 endpoint that can establish efficacy for several
19 classes of drugs intended to treat patients with
20 severe hypertriglyceridemia, greater than 500 since
21 lowering trigs in this setting is expected to
22 reduce the risk for acute pancreatitis.

1 In trial CS6, patients with familial
2 chylomicronemia syndrome or FCS assigned to
3 volanesorsen, 300 milligrams weekly, exhibited a 77
4 percent reduction in triglycerides at month 3 on
5 average in comparison with an 18 percent increase
6 among those assigned to placebo.

7 That was significant p less than 00001.
8 When efficacy is established via an effect on a
9 surrogate endpoint, however, uncertainty generally
10 remains regarding the magnitude of the drug's
11 effect on clinical benefit such as how patients,
12 feel, function, or survive.

13 The expected type and magnitude of clinical
14 benefits are important to consider when making a
15 benefit-risk assessment. We are asked to discuss
16 the efficacy, clinical benefits of volanesorsen in
17 patients with familial chylomicronemia syndrome.

18 As you can see, there's A through E. This
19 is a five-part, so I'm going to read A first and
20 then we're going to discuss. And these are not
21 voting. And then we're going to try to move
22 rapidly through the different topics. And each

1 time, I will say, can we move on to the next
2 letter.

3 Then at the end, I'm going to try to
4 summarize all of what we've done. So first, A, has
5 the applicant adequately characterized the effect
6 of volanesorsen on triglycerides to inform labeling
7 despite the proposal of a dosing strategy that has
8 not been studied in clinical trials.

9 So we're open for a discussion. Raise your
10 hand to be recognized and then we'll go through the
11 individual discussion points. And I'll be taking
12 notes and then, once we close each of these and
13 then we come back, we'll summarize. Okay?

14 Dr. Everett, did you want to start? No?

15 DR. EVERETT: Yes. I am happy to kick
16 things off. Brendan Everett. I think that, as
17 some in the committee have said, we commend the
18 sponsor for taking a medication for a rare disease
19 and putting it through a clinical testing program
20 to try and get it to market.

21 I think, unfortunately, in my opinion, we
22 don't know what we're approving here. The benefit

1 is triglyceride reduction, but we're being asked to
2 approve a dosing frequency and dose that has not
3 actually been tested in a randomized controlled
4 way.

5 So I think there's clear evidence that the
6 drug is effective at lowering triglycerides at the
7 doses tested. It's not clear to me that, that
8 would be the case or at least that the same
9 reduction would be apparent with a different dose
10 and a different frequency.

11 So I have some concerns with basically
12 approving a dose and a frequency that has not
13 really adequately been tested at all in my view.

14 DR. WILSON: Others? Yes, Dr. Newman?

15 DR. NEWMAN: I just wanted to say that I
16 agree with all of that. This dose, the dosing
17 regimen has not been tested, so we really don't
18 know its effect on triglyceride.

19 DR. WILSON: Dr. Morrato?

20 DR. MORRATO: Yes, Elaine Morrato. I'll
21 comment on the secondary endpoints. I was very
22 disappointed to see not just a statistical effect,

1 because of obviously its small sample size, but not
2 even directional clinical meaningful effects on
3 pain, on the quality of life, and didn't seem to
4 compliment where they were trying to go, and I
5 would acknowledge that FDA's encouragement in this
6 kind of situation where you're really trying to
7 weigh benefit-risk.

8 Having that kind of information would be
9 very useful at this point. So it's not just a lack
10 of small sample, but just not even a directional
11 effect.

12 DR. WILSON: Dr. Kane?

13 DR. KANE: With regard to this first
14 question, one of the things that troubles me is
15 that, in trying to interpret efficacy, there were
16 33 patients enrolled in the pivotal trial who
17 received the drug. At the end of -- and this is
18 intended, I believe, to be a chronic long-term
19 therapy and, yet, at the end of one year, only 14
20 had completed and only 6 were on the original
21 weekly schedule.

22 To me, that leaves a big gap between what

1 we're aspiring to and what we have evidence for.

2 Thank you.

3 DR. WILSON: Dr. Shamburek?

4 DR. SHAMBUREK: I agree with the discussion,
5 but I think we also have to focus that this is an
6 orphan disorder. We have limited patients. They
7 are relying upon some of their phase 2 trial, where
8 they did get a dose response, they did get a very
9 impressive 77 percent reduction in triglyceride in
10 their group in the original phase.

11 When they went to the additional extension
12 trial, they saw a similar one, so putting
13 everything else aside, I think they very well met
14 in an orphan disorder with a very unmet need, that
15 they achieved that compared to other studies.

16 DR. WILSON: Dr. Low Wang, did you have a
17 comment?

18 DR. LOW WANG: Yes. I was very impressed
19 with the degree of triglyceride lowering that was
20 seen compared to placebo at month 3 with
21 volanesorsen.

22 I think what I'm concerned about is the

1 percentage of patients who can actually tolerate
2 the treatment and sustain it. So it's a small
3 fraction, maybe a third of patients are able to
4 continue through the entire year. And so I think
5 that that's a concern. I think selection of
6 patients is incredibly important.

7 For the patients who can tolerate this
8 treatment, it could be life changing, but I think
9 being able to find those patients is going to be
10 key. But I don't think that, at the currently
11 proposed dosing strategy, we really don't have
12 enough adequate evidence for the specific dosing
13 that's proposed.

14 DR. WILSON: So what we're going to do;
15 we're trying to stay on track and we're trying to
16 create major elements for our summary for
17 discussion. And mind you, this is just 1A and we
18 have several things to go through.

19 What we're going to do is, I'm going to
20 summarize where we are at this point and then I'm
21 going to go through all of these. And then I will
22 then allow the sponsor, if there's any special

1 clarifications, once we've gotten through 1A
2 through E. Okay? So why don't we do that? Can we
3 do that?

4 I think that's acceptable to all. Yes. And
5 any other further comments? Otherwise, what I'd
6 like to do is to summarize 1A. I'd like to get
7 beyond 1A because we have a lot to discuss and
8 these topics are going to come back. Some of them,
9 we've already gotten into 1B a little bit.

10 So in summary, panel members felt that we
11 are being asked to critically evaluate and move
12 forward on a medication design and a REMS program,
13 et cetera that is not actually what has happened in
14 the trials to date. Now, this point was made
15 initially by Dr. Everett and it was corroborated by
16 Dr. Newman.

17 We also had some concerns about the
18 secondary endpoints and some of the other endpoints
19 which were not powered to fully evaluate. Dr Kane
20 mentioned that we had a considerable amount of
21 dropout in the 66 patients in the key pivotal
22 trial, especially after month 3. Dr. Low Wang made

1 the point that, especially at month 3, we had an
2 impressive triglyceride favorable effect for active
3 treatment.

4 So let's move on to B. How does the extent
5 of drug discontinuation after month 3 affect your
6 assessment of the efficacy of volanesorsen if at
7 all? Dr. Neaton?

8 DR. NEATON: I'll try. So I thought the
9 analysis that was done by the FDA, the method
10 imputation there was the appropriate one. It's the
11 one I would have done.

12 The sponsor attempted to collect the data
13 following drug discontinuation. I know that's
14 hard, but they collected it for 50 percent of the
15 people. It looks to me, at the dose that they
16 studied in the trial, there's a beneficial effect,
17 that it continues through 12 months.

18 I share the same concern actually that
19 Dr. Kane has. A sponsor said 19 people completed
20 the study. 14 of the 19 went on into the open
21 label and 5 of those had continued in the first 6
22 months, so they're kind of left with 9 out of 33

1 people.

2 So this doesn't appear to be the case that
3 this is a drug that people will really want and
4 will give up anything to take, is hard to make from
5 these data in my mind. That relates, however, in
6 my opinion, to the target population.

7 But in terms of the triglyceride effect, I
8 think it's fairly robust.

9 DR. WILSON: Any further comments on that?
10 Some of these issues, we're going to keep coming
11 back to, so I'm going to summarize what you just
12 said real quickly, Dr. Neaton, perhaps in almost as
13 many words.

14 He was concerned about the study benefit.
15 There was a study benefit at 12 months, but
16 especially there's considerable drop-off after 3
17 months. And then what is the target population for
18 this molecule in the future?

19 So let's move to letter C. Discuss whether
20 the available data provide evidence that
21 volanesorsen reduces the risk of acute
22 pancreatitis. Yes, Dr. Epstein?

1 DR. EPSTEIN: Yes. It seems like the
2 population that was studied was different than the
3 population that we heard over here because of the
4 low rate of pancreatitis and I don't think we can
5 make that correlative judgment based on this data.

6 DR. WILSON: Dr. Burman?

7 DR. BURMAN: Thank you. I agree the data
8 are certainly insufficient to definitively say that
9 the drug reduces the risk of acute pancreatitis,
10 but I would point out as a clinician and a
11 researcher that elevated triglycerides do cause
12 pancreatitis and that, if triglycerides are lowered
13 significantly, that risk of pancreatitis is going
14 to be less.

15 DR. WILSON: Yes, go ahead. Yes,
16 Ms. McCullough [sic]?

17 MS. MCCOLLISTER-SLIPP: Looking at this as
18 somebody from the consumer perspective, I mean, I
19 don't have this condition, but if I were trying to
20 decide based on what we've heard about the disease
21 itself, if I were making a risk assessment, risk-
22 benefit decision, I would take the odds of avoiding

1 pancreatitis by taking the drug.

2 I mean, it's potentially deadly. There is a
3 drop in pancreatitis. The numbers aren't very big,
4 s it's not powered the way that we would love for
5 it to be powered. But there does seem to be
6 substantial clinical benefit at least for some
7 people. We don't know exactly who those people are
8 because the numbers are so small. But I think the
9 benefit is substantial enough that the choice
10 should be available.

11 DR. WILSON: So I'd like to get a comment
12 from our other hepatologists, GI experts. Could
13 you weigh in on this and help us out? Do you agree
14 with Dr. Epstein's assessment at this point,
15 putting you on the spot, sir?

16 DR. RAUFMAN: Jean-Pierre Raufman. Evidence
17 is always a hard word. I'm not convinced that
18 we've seen evidence that the drug reduces the risk
19 of acute pancreatitis, but I can infer based on the
20 reduction in triglyceride levels that, if the study
21 were powered more strongly and there were more
22 people that we heard from in the open session, that

1 we would likely have seen a signal.

2 So I know I'm not giving a very strong
3 answer here, so no. There's no evidence. At least
4 evidence hasn't been provided, but I believe that,
5 based on what I've seen, it is likely to reduce the
6 incidence of acute pancreatitis.

7 DR. WILSON: Thank you. Dr. Everett?

8 DR. EVERETT: Just quickly, I think there's
9 a good likelihood that this degree of triglyceride
10 reduction could potentially lower the risk of
11 pancreatitis. I don't think the data that we've
12 seen support that, but I have a lot of sympathy for
13 the numbers that you would have to enroll to see
14 such an effect given the orphan disease status or
15 the rareness of the condition that's being studied.

16 I do have some more concerns, though, with
17 the actual ascertainment as an SAE ascertainment
18 rather than a different kind of more routinized
19 collection of these endpoints. You can potentially
20 run into ascertainment bias and referral bias,
21 especially when the clinicians who were caring for
22 these patients are potentially unblinded just by

1 looking at their triglyceride curve over the past
2 year or two.

3 That combines of course with the question
4 that's next to it about dropout and so you have
5 differential ascertainment on that basis, too. So
6 you begin to worry that there is potentially a
7 directional bias in terms of what kind of cases are
8 ascertained versus not, just from a trial design
9 perspective, even though I have some faith that, if
10 you were to reduce triglycerides by 70 percent, you
11 would have a reduction in pancreatitis in this
12 population.

13 DR. WILSON: Dr. Neaton?

14 DR. NEATON: Just two comments; one, I think
15 it's inconclusive, but the second, kind of
16 following what Dr. Everett said, I would totally
17 agree that basically it would have been better to
18 collect it separately and ensure that people kind
19 of understood that it was recorded through the
20 entire duration of follow-up. I've been involved
21 in too many studies where, even if the sponsor did
22 what I think they said, they collected as a serious

1 adverse event and then adjudicated.

2 Investigators at the sites just have this
3 mentality that, if you stop medication, it can't be
4 a serious adverse event anymore. So there
5 potentially is a reporting bias that differs
6 according to whether people stayed on therapy or
7 not.

8 So I don't know whether an intention-to-
9 treat analysis is appropriate here or the on-
10 treatment. I understood what the sponsor did was
11 on treatment and what I understood the FDA was a
12 better analysis on treatment.

13 I'd like to see and believe in an intent-to-
14 treat analysis, but I'm not sure that we can. But
15 in any event, it's inconclusive.

16 DR. WILSON: Dr. Morrato?

17 DR. MORRATO: My question or discussion
18 point relates to maybe the generalizability of the
19 study sample and maybe the external validity. So
20 we heard from the sponsor that I think they were
21 sizing the study, assuming 1 attack every 5 years
22 based on a literature review.

1 The FDA slide looking at the results saw
2 roughly 1 attack every 10 years and no difference
3 in rates between placebo and volanesorsen. And
4 that's different than obviously what we heard as
5 the experiences of some folks in the open. So I'm
6 trying to understand what's the general population
7 for this and others may have a sense.

8 Is that rate of 1 every 5 years about right
9 and so what we're seeing in the trial is a
10 prototypical or a typical kind of patient? Or are
11 we actually seeing a selection problem in which
12 those that came in the trial really aren't
13 representative of the clinical population.

14 DR. WILSON: Dr. Weber?

15 DR. WEBER: This is to follow up on
16 Dr. Everett's comment about the bias to
17 ascertainment. And if you've got 90 percent of the
18 folks in the trial having skin reactions on, I
19 think, the investigator's end, it was pointed out
20 by Dr. Kane before. That's pretty much an
21 indication, so that could have influenced the
22 ascertainment of pancreatic events.

1 DR. WILSON: Ms. Cuaresma?

2 MS. CUARESMA: I'll take my doctor hat off
3 for this to answer this, but I am here obviously as
4 a patient representative and I feel as though I can
5 kind of answer some of those questions because I've
6 been there done that as well as the 13 people that
7 spoke today.

8 Pancreatitis is happening way more than 1
9 time per year. And I can say that. I know at
10 least 50 people, which is almost everyone with FCS
11 right now, has been diagnosed jokingly that
12 pancreatitis is very prevalent. It's happening a
13 lot.

14 So maybe the data isn't shown here, but I
15 can say that it is happening very frequently with
16 people that have very high triglycerides. Most of
17 the patients, including my own family, are over
18 2,000 on a regular basis.

19 So if we're looking at just reducing
20 triglycerides in hopes that, that will help these
21 pancreatitis attacks or other type of FCS-related
22 issues, I think that the goal has been met. If

1 we're reducing triglycerides by over 77 percent
2 with the medication, at least we're attempting to
3 reduce the amount of pancreatitis.

4 DR. WILSON: Can we summarize? Can we move
5 on? So I'm going to try to summarize. Our liver
6 and GI specialists reminded us that we had
7 relatively lower rates and the triglyceride
8 lowering, we would expect to infer should work and
9 larger outside of this current experience and
10 moving forward with more trials and more patients.

11 We had several concerns by our epidemiology
12 clinical colleagues and patient representative
13 colleagues concerning bias, concerning blinding for
14 the administration and/or the latescence of the
15 serum, some concern about their inconclusive
16 results for some of these findings, a selection
17 bias potentially for participants in the trial.
18 Perhaps they were healthier or once they especially
19 were included within the trial, they perhaps
20 assumed healthier lifestyles.

21 That's why we may have seen lower experience
22 rates for not the primary outcome, which is

1 triglyceride change, but for the key clinical
2 outcome, which was pancreatitis occurrence.

3 I apologize for that. There's a lot to
4 summary, a lot of different comments. Any
5 amendments, recommendations? You'll get your
6 chances as we move forward here. We're only to
7 part C. 1D, discuss whether the available data
8 provide evidence that volanesorsen reduces
9 abdominal pain.

10 So this is now abdominal pain in patients
11 with FCS. Let's put our GI experts on the spot.
12 We want to hear from each of them whether they
13 think that it may reduce abdominal pain. Any
14 comment on that, Dr. Epstein, no, on whether the
15 evidence is sound that this reduces abdominal pain?

16 DR. EPSTEIN: I didn't the evidence was
17 sound.

18 DR. RAUFMAN: Jean-Pierre Raufman. I agree
19 that the evidence wasn't overwhelming and I'm not
20 quite sure what the abdominal pain is caused by. I
21 know that pancreatitis causes abdominal pain, but I
22 don't know whether we're talking about non-

1 pancreatitis pain and, if so, what's the genesis of
2 that.

3 DR. WILSON: Dr. Yanovski?

4 DR. YANOVSKI: Sure. Can I bring in quality
5 of life, too, to this? Because I don't see it
6 addressed separately. So I kind of feel a
7 disconnect here because, on the one hand, this is a
8 drug that's obviously difficult to take. Right? A
9 lot of patients didn't tolerate it or had adverse
10 effects.

11 When we heard our speakers, they almost
12 uniformly -- and this is the same population
13 because these were people who were on the drug who
14 said, "I feel better. I had so many episodes of
15 pancreatitis. I had so much abdominal pain. I
16 have so much more energy." But when we actually
17 try and look at the data in the blinded trial, we
18 just don't get that evidence.

19 I was struck by the fact that about half of
20 people didn't even report significant abdominal
21 pain prior to the study, and that so few reported
22 abdominal pain during the study, and that there was

1 no difference, and that there was also no measured
2 difference in quality of life.

3 So given that there's serious adverse
4 effects and it's a really difficult medication to
5 tolerate, I would really like to see some evidence
6 that patients feel or function better on the drug.

7 DR. WILSON: Yes. Just Ms. Cuaresma is
8 next.

9 MS. CUARESMA: Yes. I actually had written
10 that same thing down. When you look at the slides
11 CS6, the full analysis study and then the quality
12 of life, the weighted sum seems insignificant.
13 However, I'd like to point out that we heard it
14 firsthand here, so I don't know where the
15 discrepancy is or why it's so different, but these
16 are the people on the drug, and they're reporting
17 that they are feeling better, and that their
18 abdominal pain has lessened, and that their quality
19 of life is better.

20 So I agree there was kind of a disconnect in
21 some of the slides in some of the information that
22 was given, but I just want to make sure you've

1 heard it firsthand here that it is helping the
2 patients that are taking it.

3 DR. WILSON: Dr. Weber?

4 DR. WEBER: Part of the explanation is that
5 we saw a biased sample. There were 33 subjects in
6 the study and I think we heard from 6 today, so we
7 may have had their positive effects as opposed to
8 neutral effects.

9 DR. WILSON: Who is next? Dr. Morrato and
10 then McCollister? Dr. Morrato?

11 DR. MORRATO: I'd just like to underscore
12 that. I was going to make that same comment. I
13 think we have to also remember that three-quarters
14 of the patients withdrew from the study, so they
15 obviously also had their experiences that didn't
16 get to be voiced here.

17 DR. WILSON: Ms. McCollister?

18 MS. MCCOLLISTER-SLIPP: I found that the
19 evidence of decreasing abdominal pain to be pretty
20 much non-existent, but I think the company spoke to
21 this. And I don't know the specific measures or
22 questionnaires that were referenced. I'm not

1 familiar with them, but I'm familiar with
2 questionnaires used in other conditions for studies
3 that I have been involved in and most of them are
4 not particularly good.

5 So I think we need to be aware of the fact
6 that, just because these particular instruments or
7 patient-reported outcome questionnaires didn't
8 measure something doesn't necessarily mean that
9 there isn't a reduction. And I completely agree,
10 you don't fly across the country to go on FDA
11 advisory committee and just say that the drug is
12 not good.

13 Generally, it creates a bias of bringing
14 people in. You get excited about something that
15 benefits your life, but I do think that we need to
16 acknowledge and the company has acknowledge that
17 these particular instruments may not be sensitive
18 or may not be tuned with the specific types of
19 abdominal pain that might be present in this
20 population.

21 DR. WILSON: Dr. Newman?

22 DR. NEWMAN: I just wanted to mention that

1 abdominal pain is very subjective and the only way
2 to evaluate that is in a placebo-controlled trial.
3 And that may explain some of the differences we see
4 in these data compared to what other people spoke
5 about today.

6 I didn't think there was an effect on
7 abdominal pain in this particular study.

8 DR. WILSON: Dr. Neaton?

9 DR. NEATON: I just was going to bring it up
10 earlier, but since we're talking about quality of
11 life, the sponsor did this trial largely outside
12 the United States. And they said they're working
13 on a quality control, quality of life instrument
14 that's more suitable for this population, but in
15 studies that I've done internationally, you have to
16 be very conscious of the culture that you're even
17 giving the questionnaire in.

18 So I don't know to what extent the large
19 population outside the United States may have had
20 some impact on his findings.

21 DR. WILSON: Dr. Low Wang?

22 DR. LOW WANG: So one of the other comments

1 I wanted to make is that I didn't expect to see a
2 difference in the questionnaires because I think
3 that the sensitivity is very low with such a small
4 population.

5 So I would have been extremely surprised if
6 there had been a difference between the populations
7 in terms of quality of life as measured by these
8 questionnaires.

9 So given that, I think that the available
10 data don't provide evidence that volanesorsen
11 reduces abdominal pain in these patients, but if I
12 could move on to E, I do have to say again that I
13 think that, in terms of the magnitude of
14 triglyceride lowering in the patients who can
15 tolerate, and can stay on the treatment, and can
16 sustain this, that degree of triglyceride lowering
17 of 90 some percent compared to placebo is expected
18 or has the potential to improve their quality of
19 life and reduce their risk of pancreatitis.

20 So I do think that, in terms of overall
21 magnitude of clinical benefit for the patients, the
22 right patients, so I think selection of the right

1 patient population is incredibly important. It
2 could be of benefit and I think that's a key point
3 for an orphan drug.

4 DR. WILSON: So I'm going to try to
5 summarize this rather rapidly because some of these
6 issues are going to come up again. We started out
7 with a very simple question, whether this reduced
8 abdominal pain, and our GI experts especially said
9 the data were not convincing that it did reduce.

10 Then we had an add-in, what about the
11 quality of life, and we spent most of this time
12 discussing quality of life. And we had a variety
13 of interpretations, including a difficulty
14 assigning what is a quality of life in different
15 cultures and different populations.

16 I think also concern about the quality of
17 life types of questionnaires. Instruments are
18 difficult to assess in the population sizes that
19 were studied here.

20 So let's move on to the next E point. I
21 believe that's our last one for this. Considering
22 both the benefits that you expect based on the

1 magnitude of triglyceride lowering as well as what
2 was observed in the development program, how would
3 you characterize the overall magnitude of clinical
4 benefit that results from treatment with
5 volanesorsen?

6 This is sort of putting it all together.
7 Here, most of this is a summary for this question.
8 Dr. Shamburek?

9 DR. SHAMBUREK: I waited for this question
10 just to summarize the pancreatitis, the abdominal.
11 I think the real key in familial chylomicron
12 syndrome is getting the triglyceride under 1,000.
13 Volanesorsen reduced the triglyceride 77 percent,
14 but I think more importantly, the triglyceride went
15 from 2,267 to 590. That's a magical number.

16 People who have followed these patients'
17 natural history and those who could tolerate diet
18 and who were under 1,000 did well. So I think, at
19 the beginning, I was absolutely convinced that
20 there would be a favorable impact on clinical
21 manifestations based on the natural history.

22 However, the study itself, the CS6 pivotal,

1 I am not convinced showed that. And I think some
2 of that, we've heard of the powering and design.
3 The patients were 46. The patients that we heard
4 start young and have repeated bouts. Some of those
5 go on to chronic pancreatitis. Some of them get
6 the endocrine, exocrine.

7 The older group is -- in one sense, if we're
8 saying one episode every 5 years is a lower-risk
9 population, not that it's not significant.

10 If we had a higher risk one, we've heard on
11 the internet people coming in, several people
12 having 30, 50 episodes of pancreatitis. We almost
13 need, like with smoking with pack-years, a
14 pancreatic score where you've had several.

15 Had there been either one of two things, one
16 where you had people who are out there -- and I
17 think it's part of the group with multiple
18 relapsing -- we would have seen it in a 1- or 2-
19 year study.

20 Otherwise, this other one that's getting 1
21 in 5, there's no way in a 1-year study you could.
22 So I personally think the study did not show that,

1 but I think the drug should, based on
2 epidemiology -- and again, we don't have the
3 evidence -- would end up helping abdominal pain and
4 pancreatitis, but there's that population
5 limitation.

6 DR. WILSON: Dr. Newman?

7 DR. NEWMAN: I'm not sure some of what was
8 just said, but I do think that the drug lowered
9 triglycerides and that it will do so with another
10 dosing regimen that hasn't been studied yet. And I
11 think that will confer a clinical benefit on the
12 patients that have familial chylomicronemia
13 syndrome.

14 So even though this clinical benefit was not
15 demonstrated in this phase 3 program, I believe
16 that there will be a benefit because of the
17 significant triglyceride reduction.

18 DR. WILSON: Yes, Dr. Epstein?

19 DR. EPSTEIN: It's incumbent upon the
20 sponsor when they first design the study and 90
21 percent of the problems occur in the original
22 design. And there was inclusion issues here.

1 There was study design issues throughout. There
2 were flaws in the study. And part of that's
3 because of the small orphan drug. It's very hard.

4 But that was a flaw and they didn't get the
5 right population, which I think everyone here has
6 said. So we look at two things, safety and
7 efficacy. And here, they demonstrated only the
8 reduction in the level of triglycerides at 3
9 months. They did not demonstrate the efficacy to
10 treat the patients like we heard that's missing.

11 DR. WILSON: Yes, Reshma. Go ahead. And
12 say your full name. I apologize. I'm good with
13 your first --

14 DR. KEWALRAMANI: No problem. Reshma
15 Kewalramani. I just want to put a fine point on
16 the fact that, as designed, the study was powered
17 for a decrease in triglycerides at the 12-week time
18 point.

19 As such, which is what's on page 59, I
20 didn't have an expectation that, in this small
21 number of patients, we would be able to see beyond
22 triglycerides because the numbers are small and it

1 is powered for triglycerides.

2 The fine point I want to put on that is
3 simply that the study was overwhelming positive on
4 the primary endpoint as it was described to be.

5 DR. WILSON: Any further discussion?

6 DR. KANE: Yes.

7 DR. WILSON: Yes. Dr. Kane?

8 DR. KANE: Kane. Just to carry this
9 forward, then, we're asked to comment on the
10 clinical benefit as demonstrated in the information
11 that we have on hand and the primary endpoint is 12
12 weeks of triglyceride reduction.

13 No one is disagreeing with that, but I think
14 everything beyond that is a bit of a leap of faith.
15 Thank you.

16 DR. WILSON: Dr. Morrato?

17 DR. MORRATO: Yes. Just to get back to
18 Dr. Epstein's point, I was struck by the
19 repeatedness of the FDA's advice to the sponsors to
20 be addressing the design issues of these other
21 secondary endpoints, knowing in light of the full
22 benefit, efficacy benefit-risk profile. So I would

1 agree that it met its primary, but I also think
2 it's the study and the sponsor fell short of
3 meeting the FDA's suggestions to be addressing this
4 when they had their post-phase 2 meeting.

5 DR. WILSON: I'll try to summarize. You get
6 your chances to edit whatever I say here. So
7 Dr. Shamburek started this section off here. The
8 key was that the triglyceride lowering was really
9 quite remarkable for patients who were enrolled and
10 especially given their age.

11 They've survived to a greater age than many
12 of the patients we expect to have this and who
13 might have more severe symptom and more severe
14 triglyceride problems at a younger age.

15 Almost every person who spoke to this felt
16 that we could infer clinical benefit, but we have
17 not observed that. The emphasis was especially
18 placed on the 3-month result rather than what
19 happened starting 6 months, 9 months, 12 months
20 when there were trial modifications, which kept our
21 confidence up for inference, but we do not have
22 solid proof to put our fingers on the data to say

1 that there's definite benefits because of various
2 changes.

3 Why don't I leave it at that? Any further
4 edits? We're ready for question 2. So I've been
5 informed from the sponsor if anybody from our
6 committee needs any specific clarifications, we can
7 turn to the sponsor at this point, but the
8 sponsor's really generally not part of -- is there
9 anything that we've misstated?

10 The sponsor's asking for the floor, but
11 other than that, only a clarification, I believe at
12 this point, because you're not part of the
13 discussion.

14 DR. O'DEA: Understood. So the
15 clarification is around the dosing regimen. I just
16 wanted to point out that, that is the dosing
17 regimen that was used in the CS6, continues to be
18 used in CS7.

19 We have about 60 patients who have been
20 treated with this dosing regimen and the only
21 addition now is to add a weight-based dosing
22 element to that paradigm. So it's the established

1 paradigm that we've been using throughout.

2 The other thing is, there was a comment
3 about three-quarters of the patients dropped out,
4 60 percent of the patients completed, and currently
5 in the continuing long-term trial, 80 percent of
6 the patients are retained.

7 DR. WILSON: Thank you very much. So we'll
8 move on to question 2. Aside from
9 thrombocytopenia, discuss the tolerability and
10 safety of volanesorsen such as injection site
11 reactions, immunogenicity, hypersensitivity, liver-
12 related safety, renal-related safety, and any other
13 safety concerns.

14 But to hold off on thrombocytopenia as I
15 understand, we're not going to remember that, so
16 we're not going to talk about platelets. So let's
17 first hear about any reactions concerned about
18 those first ones, injection site. Dr Newman?

19 DR. NEWMAN: I think we all saw that that
20 there were injection site reactions in the patients
21 who were allocated volanesorsen. These included
22 discoloration of the skin, erythema in duration,

1 pain, and itching

2 They did not always resolve. And also there
3 were some hypersensitivity reactions and I will
4 wait to discuss liver and renal.

5 LX Thank you. Dr. Epstein?

6 DR. EPSTEIN: Yes. Having reviewed trials
7 of biologics and other injectables, these are high
8 rates. These are way above what I've seen with any
9 other trial.

10 DR. WILSON: So your concern is that the
11 percentage of injection site reactions is greater
12 than you might expect from other biologics that
13 would be used to treat, for instance,
14 gastrointestinal diseases.

15 DR. EPSTEIN: They typically hover around 5
16 to 8 percent. Here, we have 87 percent.

17 DR. WILSON: Dr. Budnitz?

18 DR. BUDNITZ: Dan Budnitz. I agree with the
19 comments about injection site reactions, but in
20 terms of understanding the safety of these other
21 adverse events; immunogenicity, hypersensitivity,
22 liver, and renal, I think just our safety database

1 is just so small it's hard to say much of anything
2 with under 100 patients with a high dropout rate,
3 but that's where we are. So we'd need more of a
4 safety dataset.

5 DR. WILSON: Dr. Burman?

6 DR. BURMAN: Thank you. I'm just also
7 concerned about the presence of antibodies and what
8 role they may play in abrogation of the effect or
9 any other immunologic response.

10 DR. WILSON: To follow up on that,
11 Dr. Burman, your concern about the antidrug
12 antibodies and what that might mean over time; is
13 that where that's going?

14 DR. BURMAN: Yes. Thank you.

15 DR. WILSON: What would you want to see in
16 the future, for instance?

17 DR. BURMAN: Definite measurement of
18 antibody with their titer and then nice detail
19 correlation with benefit for the drug, to make sure
20 it's not abrogating the effect.

21 DR. WILSON: So you've already moved a
22 little bit into the immunogenicity, but that may be

1 related to injection sites as well. So to follow
2 up on what Dr. Burman's already getting us into,
3 immunogenicity, any specific questions there or
4 comments, I mean, or understanding of where we are?

5 Is there concern about the antibody titer
6 development? Dr. Epstein?

7 DR. EPSTEIN: So with antibody titer, it's
8 very important to fully understand because, for us,
9 with the biologics, for decades, we did not know
10 what was going on with the antibodies. And we
11 later determined they cause secondary loss of
12 response to the drug.

13 So e would have people dropping off because
14 the antibodies were building up early. We weren't
15 using the proper dose.

16 So you need to do therapeutic drug
17 monitoring, which is your antibody levels, your
18 drug levels early, early, sort of in the induction,
19 if you will, and determine whether or not you have
20 an antibody former or not. And those patients
21 require dose adjustments.

22 They require sometimes secondary medications

1 and they can also be at risk for other adverse
2 events, hypersensitivity reactions, antibody
3 reactions, flu-like symptoms, immunogenicity, and
4 even anaphylaxis.

5 DR. WILSON: To follow up on some of these
6 immunogenicity issues, have we seen enough over
7 even 1 year for pause and restart? The sponsor did
8 show information on that. We don't have much data
9 beyond 1 year. These trials are largely short term
10 as opposed to 3- or 4-year types of safety data for
11 antibody development, so that's another comment to
12 build on Dr. Epstein's.

13 Yes, Dr. Kane?

14 DR. KANE: Kane. In my experience with
15 this, this frequency of antidrug antibody is not
16 that unusual. I'm not particularly troubled by
17 this event. Neutralizing antibody would be a
18 different story or if we had a closer implication
19 of a particular subgroup of antibodies to the
20 thrombocytopenia, that might be a different story.
21 That's not the case here, from what I can see.
22 Thank you.

1 DR. WILSON: Let's move on to
2 hypersensitivity. Any comments on
3 hypersensitivity? None specific? Dr. Epstein, did
4 you want to make a comment on it, you think?

5 DR. EPSTEIN: Just that anaphylactic rates
6 should be about 0.1 percent, so should these
7 patients be carrying an EpiPen? Obviously, this
8 patient had to have epinephrine. They're at home.
9 Where are they getting it? Who is injecting them?
10 Anaphylaxis is very, very serious.

11 There is going to be a rate with any
12 injectable, that's true, but it should be quite
13 low. We don't know those numbers. And also, we
14 have somebody with serum sickness, which is a very
15 damn serious disease, a very life-threatening
16 disease, and so we have now two of these in a small
17 number of patients. But we don't know what that
18 means.

19 DR. WILSON: So I'll cut to that in a
20 summary, but you can guess it's going to be we need
21 more information. But for instance, I don't know
22 what to say. I don't think any of us know when we

1 have only one of each sort of is a major problem.

2 Liver-related safety? Our hepatologists,
3 yes?

4 DR. RAUFMAN: I don't think there was a
5 signal for liver or kidney. I didn't hear anything
6 significant.

7 DR. WILSON: Dr. Epstein concurs, I believe.
8 And renal-related safety? Dr. Low Wang?

9 DR. LOW WANG: So I was surprised at the
10 degree, at the number of renal events, the renal
11 adverse events in the volanesorsen-treated patients
12 compared to placebo. So on both the worsening
13 proteinuria, the worsening creatinine, the overall
14 rates were a lot higher, so that was concerning,
15 albeit the numbers were small.

16 DR. WILSON: Any other safety concerns?

17 (No response.)

18 DR. WILSON: Ms. Sinclair, I'm sorry. I
19 apologize.

20 DR. SINCLAIR: Hi, Susan Sinclair. I think
21 that I won't speak to the specific signals and
22 whether I think they're important or not, but I do

1 think, like is previously stated, that the safety
2 database is too small.

3 However, there are data being collected
4 right now in the open-label extension that could
5 inform this. It'd be helpful to get a look at
6 that. Also, when I think about the quality of
7 life, I think about patients who, initially, are
8 coming to terms with, maybe I don't have to worry
9 about pancreatitis so much now, so it takes a while
10 to maybe come to terms with that.

11 Maybe that's not reflected immediately in a
12 quality of life instrument. However, if there's
13 flu-like symptoms, fatigue, and maybe inconvenience
14 going in for blood draws and traveling to a site,
15 that could maybe offset some of the quality of life
16 improvements that you would hope to see.

17 Also, those instruments, though, are well
18 validated in multiple languages across the world,
19 but then again, the sample size is small.

20 DR. WILSON: I'm going to summarize this.
21 There is concern about injection site reactions
22 were greater in the active treatment arm with

1 volanesorsen versus the placebo. And it was not
2 just a mild increase. It was a rather large
3 increase in comparison to others that have been
4 used for biologic injectables.

5 There was less concern about the
6 immunogenicity, specifically the antidrug
7 antibodies. There was definitely some concern
8 because, although rare, there have been some
9 hypersensitivity reactions, especially with at
10 least 1 case of anaphylaxis and 1 of serum
11 sickness.

12 There was no real concern for liver-related
13 safety. There is some signal for renal-related
14 safety on the other hand and that perhaps should be
15 paid a little bit greater attention moving forward.
16 And no other specific safety concerns were brought
17 up.

18 So at this point, it is five minutes to
19 4:00. You're going to get a five-minute break
20 basically to have a biologic break. And please
21 come back so that we can finish up on time. Thank
22 you.

1 (Whereupon, at 3:55 p.m., a recess was
2 taken.)

3 DR. WILSON: We're going to try and get
4 going in a couple of minutes, so let's please take
5 your seats. Okay. Please take your seats and the
6 start of this. We're now up to question 3 and I'll
7 tell you what's going to happen between now and our
8 target is to end at 5:00.

9 We're going to have question 3, question 5,
10 and question 7. Question 4 will be visited as part
11 of the vote and, if we have time after question 7,
12 we will come back to pediatric issues with question
13 6. So we're going to move on to question 3, so if
14 we could pull that up.

15 So discuss the risk for thrombocytopenia and
16 bleeding associated with volanesorsen. And A is,
17 discuss your level of concern for the risk of
18 thrombocytopenia and bleeding with chronic
19 treatment with volanesorsen. I'll stop there.
20 Let's do A first.

21 Open for discussion. Yes, Dr. Ortel?

22 DR. ORTEL: So if I can lead off, Tom Ortel,

1 the way that I just approach part A, which is not
2 the monitoring or the parts B and C, just when you
3 talk about level of concern, I'm looking at the
4 thrombocytopenia from the perspective of the way
5 that Dr. Roberts described it, that there's two
6 types.

7 There's this slow type that seems to be
8 something that, if you're monitoring, you should be
9 able to catch, you should be able to intervene. So
10 I'm not really worried about that. That is
11 something that you can catch.

12 The second one, though, is a little bit more
13 concerning, the one where it can precipitously
14 drop. The only thing that I would say about that
15 is that, really, a monitoring system -- it's very
16 difficult to catch that because, as some people
17 mentioned, that's an idiosyncratic event. You
18 don't know when it's going to happen.

19 But looking at the numbers that were
20 provided of the 8 patients that had the severe
21 thrombocytopenia, 4 of them were in the 40,000
22 range, which is not a number I would even treat

1 necessarily. So I'm not as concerned about that,
2 but these people are not dropping severely low.

3 Only one of them dropped below 10, which is
4 again where I put my marker for what I would be
5 concerned about, spontaneous bleeding. That's the
6 thrombocytopenia part.

7 The bleeding part is interesting because I
8 think it's divorced from the platelet count. It
9 isn't that there's a clear relationship between a
10 platelet count and the bleeding manifestations,
11 suggesting that there might be something else also
12 going on here, either with some qualitative
13 platelet defect or some other kind of thing that's
14 separate, but fortunately, we didn't get a lot of
15 bleeding symptoms that were fatal bleeding outcomes
16 or major bleeding outcomes, so I think that you
17 have to look at that separately.

18 So if I look at them all separately, I'm not
19 as concerned about it as it was initially put
20 together.

21 DR. WILSON: Dr. Stroncek, over here?

22 DR. STRONCEK: Yes. Hi. This is Dave

1 Stroncek. I agree that this type 1
2 thrombocytopenia is not as much of a concern
3 because it can be picked up and it's slow. I do
4 have a concern about the type 2 thrombocytopenia.
5 It looks like it will happen.

6 Even anything below 50,000 people do have
7 prolonged bleeding time. So I think, if you give
8 this drug to enough people long enough, someone
9 will have a serious bleed. And I don't see any way
10 to eliminate that risk with this drug.

11 DR. WILSON: Dr. Kane?

12 DR. KANE: I share a lot of the same
13 expressions we just heard here and I also focus on
14 the severe precipitous thrombocytopenia.
15 Fortunately, there's been no clinically important
16 bleeding in a carefully constructed and conduct a
17 clinical trial.

18 I think it's one or two orders of magnitude
19 different in the population, even including a REMS
20 because we don't really know that the REMS is going
21 to achieve what we hope it will. The devil's often
22 in the details.

1 So to me, the 8 patients in total with FCS
2 developed the below 50,000. And in the two most
3 direct clinical trials, CS6, CS7. There are 6 out
4 of 76 patients below 50,000. I think, to me,
5 that's a high risk. Thank you.

6 DR. WILSON: As a non-hematologist, what
7 about the threshold that have been used for the
8 studies up to now? Dr. Ortel's especially not so
9 concerned with a 10 to 30, but there's been a lot
10 of highlighting in the write-ups that we've seen
11 for lower numbers and also whether thresholds at
12 which time the medications were given or not given.
13 Could you help us?

14 Before we get to a voting question, this
15 would later potentially relate to that. But what
16 do you think of the thresholds that have been used
17 in the development program up to now?

18 DR. KANE: If I could continue on, then, I
19 think the thresholds that you're looking at are
20 defined mostly by the adverse events reporting
21 system. Below 50,000 is considered to be severe.
22 And to me, that's where the concern really rises.

1 I think also, in a more general population,
2 there are going to be other conditions, drugs,
3 diseases, co-morbidities adding to the risk for
4 thrombocytopenia. Also, there's not a close good
5 correlation that I know of between a particular
6 platelet count on a particular day and the actual
7 risk that, that individual is going to bleed, so I
8 think we've got a loose correlation, but simply
9 more or less a warning sign her.

10 The other point I would say; the bruising,
11 the epistaxis, the gingival bleeding probably,
12 compared to the importance of this treatment, are
13 not that important in and of themselves. Thank
14 you.

15 DR. WILSON: Dr. Shamburek?

16 DR. SHAMBUREK: Yes. I'm not going to
17 repeat anything. The bleeding thing worries me a
18 little bit because of the unpredictability and then
19 we had our experts talk about the platelet. But I
20 think my most feared complication in these patients
21 is necrotizing hemorrhagic pancreatitis.

22 If volanesorsen prevents it and we don't

1 have it, that's good, but patients who develop this
2 and end up having very low platelets might not have
3 very good outcomes. So I mean, that's just
4 something to think about. We haven't seen that,
5 but that's where the platelet or bleeding problem
6 could become an issue in the treated patients.

7 DR. WILSON: Dr. Ortel?

8 DR. ORTEL: Tom Ortel. Also following up on
9 some of the things Dr. Kane mentioned, I agree
10 that, when you put this drug out in the real world
11 and people are using it. When I'm talking about
12 platelet counts and where I get concerned about it,
13 it's in the patient who hasn't got anything else on
14 board. It's just platelet count and looking at the
15 platelet count and where it goes.

16 When you put a situation where the patient
17 may also be taking an aspirin or they have
18 pancreatitis or they have something else, then the
19 numbers become more important as far as once you
20 drop below that 50. So using it as a target is
21 reasonable.

22 DR. WILSON: Yes, Dr. Epstein?

1 DR. EPSTEIN: From a hematologic standpoint,
2 it's true that 10,000 or below is when you get
3 spontaneous oozing of blood from all of the mucosa
4 in the body. But at 50,000 is when you see
5 patients that might take an aspirin or Naprosyn or
6 they're on Plavix or another antiplatelet drug or
7 an anticoagulant, coumadin, or what have you.

8 That's where you get massive GI hemorrhages
9 and we have enough trouble because we get called
10 and I know this data is not in this study, but this
11 is real world. We get called every night for these
12 bleeds, maybe 2 or 3 times a night for GI bleeds,
13 and it's always the same story. And if they have a
14 platelet count below 50, we're not going to be able
15 to stop that bleeding with our hemostatic methods.

16 So that's a real concern. And I didn't see
17 in the REMS and I was looking for this, that they
18 controlled for aspirin, and non-steroidals, and
19 anticoagulants, and for antiplatelet drugs.

20 DR. WILSON: Can we try to summarize this at
21 this point? We started off discussing this issue,
22 3A, with Dr. Ortel's comments. He favored the

1 approach with the type 1, which he thought is
2 somewhat trackable and intervenable.

3 Type 2 for low platelet count is
4 idiosyncratic and a concern. He has a little bit
5 less concern clinically if there is less. The
6 greater concern is that the platelet count is less
7 than 10,000, but agreed with the monitoring systems
8 in place, especially to raise flags when 50,000 is
9 reached, but there seems to be some element of a
10 gray area between 10,000 and 50,000.

11 All of the commenters made the point that
12 there seems to be a disconnect between bleeding
13 episodes and individuals' specific platelet count.
14 And there was a wish for greater information on co-
15 morbid conditions and medications or conditions
16 that may especially affect platelet count or
17 platelet function and other hematologic function as
18 we move forward to a wider use of this medication
19 and especially what would happen for individuals
20 taking antiplatelet drugs or drugs that affect
21 platelet numbers or function.

22 So that's most of what I had. Any comments,

1 extra edits?

2 (No response.)

3 DR. WILSON: No. All right. So let's go on
4 to part B. The applicant has proposed labeling
5 that recommends intensive platelet monitoring. I'm
6 sorry. I'm going to have to read this on my copy,
7 not on the screen because it runs off, such as a
8 minimum of every two weeks for the duration of
9 treatment with this potentially lifelong therapy.

10 Discuss whether the proposed frequency of
11 monitoring adequately addresses the risk of
12 thrombocytopenia and bleeding as well as whether
13 such monitoring would be feasible in clinical
14 practice. If you disagree with the proposed
15 monitoring scheme, discuss how patients treated
16 with volanesorsen should be monitored for
17 thrombocytopenia or bleeding if approved.

18 Dr. Ortel?

19 DR. ORTEL: Tom Ortel. I think that some
20 monitoring plan is appropriate for this type of
21 drug as far as monitoring platelet counts. I think
22 monitoring every two weeks might be more than you

1 need for this slow drop. I think monitoring every
2 two weeks is not necessarily going to pick up an
3 idiosyncratic reaction.

4 It's hard to say what's the sweet spot for
5 what would be the right frequency with which you
6 want to be checking the platelet count on these
7 because those two are completely different things,
8 but you do need some kind of monitoring in place
9 while the patient's taking the drug.

10 DR. WILSON: Dr. Everett?

11 DR. EVERETT: Yes. I want to echo
12 Dr. Ortel's comments. I also want to say that
13 measuring something every two weeks within the
14 context of a highly structured, very focused
15 clinical trial is very challenging. It's much more
16 challenging to do on a routinized and reliable
17 basis in general clinical practice.

18 So I think that, even if you proposed to
19 check platelets every two weeks, the reality is
20 that it might happen for a couple of the patients
21 on these medications, but the vast majority are not
22 going to be able to have that rigorous platelet

1 ascertainment.

2 It's going to be a challenge. If you think
3 it's important to evaluate platelets every 2 to 3
4 weeks, it's going to be difficult to actually
5 maintain that frequency of platelet ascertainment
6 in general clinical practice.

7 I share Dr. Ortel's concern that it doesn't
8 seem to prevent the possibility of a precipitous
9 drop in the clinical consequences thereof as well.
10 I do think it's necessary to have such a plan,
11 have.

12 DR. WILSON: Dr. Budnitz?

13 DR. BUDNITZ: Dan Budnitz. I agree with the
14 comments before. Just in my mind, the two-week
15 monitoring isn't so much to prevent the precipitous
16 drop, but to limit the amount of time that a
17 patient is hanging out at less than 10,000
18 platelets. So I see the point that every two weeks
19 might not be as clinically feasible, but you don't
20 want those patients hanging out for 8 weeks when
21 they have intercurrent medications added to their
22 regimen and other things going on.

1 Just we wonder if either the FDA or the
2 sponsor might have a recommendation on when this
3 two-week testing happened. Does it happen 48 hours
4 before the next dose? Does it happen 48 hours
5 after the next dose? I don't quite know the
6 mechanism of action and when an appropriate time
7 would be, but maybe if there could be such a
8 recommendation, that would be helpful to folks.

9 DR. WILSON: Any further comments? Yes.

10 MS. MCCOLLISTER-SLIPP: Speaking from the
11 perspective of the patient again, I don't have this
12 particular condition, but I have others. I think
13 every two weeks is going to be incredibly
14 burdensome and very difficult.

15 My hunch is that, over time, as people get
16 used to the medication and they've been on it for a
17 while, they're going to be really irritated by the
18 fact that they have to make it to the determine
19 every two weeks to take this medication. I don't
20 live with the disease. I don't know what the
21 relative constraints are on the way you live
22 currently.

1 So I think that's really important, to be
2 able to let people to make that decision as opposed
3 to somebody like me, but it might be the kind of
4 thing where I know there are companies now that do
5 in-home blood draws. That might be something that
6 could be coupled with a REMS strategy if it really
7 is that clinically important, to make sure people
8 don't hang out at a low level of platelets.

9 I don't have the expertise to assess that
10 importance, but I think, from a practical
11 perspective, it's going to be really difficult to
12 sustain over any period of time. And we don't have
13 the data to, like, provide any long-term guidance
14 about how long that needs to happen just because
15 it's a small population, it's a new drug.

16 But I don't think it's all that feasible. I
17 mean, I don't think it's realistic that that's
18 going to happen on a regular basis.

19 DR. WILSON: Dr. Morrato?

20 DR. MORRATO: I would like to build on that
21 and I think also you raised a question earlier as
22 to how do you know if that's the dosing schedule

1 for the rest of the life of the drug, too. So
2 there are examples of drugs like clozapine in which
3 its regular counts.

4 Also, there was supposed to be regular liver
5 function testing with statins, so there are other
6 examples. And often, what happens? You get
7 something in the label and it's used. And then you
8 get data and, years later, you're changing it.

9 I think this would be a good case in which
10 this is also enhanced pharmacovigilance, the way
11 the sponsors have talked about it. And I would
12 rather see some prospective discussion around what
13 data, information would inform label changes.

14 So that's sort of prospectively built in, so
15 as the pharmacovigilance is coming in, it can be
16 more updated over time. So I know it's not
17 uncommon that, if you've made it through a year at
18 this thing, maybe we can make it down to four weeks
19 and your year 2 and beyond, et cetera. And so
20 build it into the design up front rather than
21 saying this is it, forever.

22 DR. WILSON: Yes. So Dr. Morrato, thank

1 you. I wanted to build on her comment and there
2 was a question back to our pharmacologist and
3 hematologist. Is this concern about type 2 that
4 much of an issue? For instance, if your platelet
5 count is above 100,000 and you're going along
6 100 to 150,000, might you still be at risk for this
7 severe drop?

8 Do you have any opinions, any of our
9 hematologists or pharmacologists on that?
10 Dr. Ortel?

11 DR. ORTEL: I didn't get the impression from
12 the data presented that, if you started out a
13 little bit lower, you were more likely to have a
14 precipitous drop than if you started out a little
15 bit higher.

16 That was from those figures that you showed.
17 I don't think there was any correlation with where
18 you started.

19 DR. WILSON: Yes, and we also only have a
20 handful of cases for this as well, but thank you.
21 I think that's going to be a question that's going
22 to always come up. Any others? Yes, go ahead.

1 MS. CUARESMA: Sorry. Go ahead.

2 DR. WILSON: Dr. Ortel, go ahead and finish
3 up, though.

4 DR. ORTEL: So just to follow up on the
5 questions on monitoring and coming in and getting
6 monitored, speaking from the standpoint of somebody
7 who runs an anticoag clinic, patients do come in
8 and get their INRs checked. If they don't come in,
9 they don't get their meds. Patients with sickle
10 cell have to come in and get their counts checked
11 or they don't get their Hydrea or they don't get
12 their pain meds.

13 I mean, there are ways that you can link not
14 giving the patient a year's worth of medication and
15 then tell them to come in every 2 to 4 weeks. So I
16 think that there's ways that you can do it and
17 patients complain about coming in to get their INR
18 checked, I guarantee you, but they do it.

19 DR. WILSON: Thank you. Dr. Weber?

20 DR. WEBER: Just a question for the group,
21 for the hematologists. It may reduce the burden of
22 having to do this. Is there point-of-care testing

1 for platelets that would make it more simple or is
2 that not widely available?

3 DR. ORTEL: I don't think there's a point of
4 care for platelet testing, but there's also nothing
5 that says you probably won't see this occurring in
6 your local pharmacy. They'll have the walk-in-and-
7 get-your-platelet-count-checked.

8 They're doing everything else in pharmacies.
9 Amazon will probably do it soon.

10 DR. WILSON: Ms. Cuaresma?

11 MS. CUARESMA: So that actually was where I
12 was going to go just as a patient perspective
13 again, to go in every two weeks. We do that now
14 and, just as what you said, if a patient is
15 suffering, they'll go in every two weeks to get
16 their medication.

17 So maybe for some patients, but the majority
18 I feel will make it in every two weeks for them to
19 be able to get the medication.

20 DR. WILSON: Can we summarize this at this
21 point? So the question is related to how often to
22 monitor. And most of the panel felt that two

1 weeks' interval is fine. And this is practicable,
2 but is burdensome. And the question has been
3 raised especially by our consumer advocates and
4 experts at the science level is, couldn't we find
5 ways to perhaps lengthen that interval for some
6 individuals.

7 Then the question also comes up for how we
8 might get better at detecting the people who are
9 especially at risk for this type 2 drop in platelet
10 count. And we're still vexed, I think. We're
11 challenged for how to find a solution to identify
12 those people before an event might occur.

13 The one last thing I think is that there is
14 some tension about whether patients and providers
15 can work together for two-week intervals. The
16 hematologists remind us that this is common for
17 warfarin dosing. Patients who are successful; it
18 can be linked to the medication refill.

19 So let's move on to the next one, letter C.
20 The applicant has proposed a dosing algorithm that
21 recommends a dosing frequency based on platelet
22 level and body weight. Discuss whether the

1 available data in the clinical development program
2 are adequate to inform dosing recommendations for
3 labeling and would ensure the safe use of
4 volanesorsen.

5 Dr. Ortel?

6 DR. ORTEL: Tom Ortel. So I think that a
7 dosing algorithm strategy makes sense conceptually.
8 I think that the data that they've got to support
9 what they're proposing is extremely limited, but
10 again, it's very small numbers, but some kind of
11 dosing adjustment is reasonable.

12 We do it for other medications where we're
13 treating patients with thrombocytopenia or
14 thrombocytosis. So that concept is there. The one
15 thing that's not mentioned in here, but that I do
16 have a significant problem with is the concept that
17 the recommendation for a treatment is made with
18 steroids.

19 I think that we need to educate the
20 hematology community about the medication so that
21 they know how to treat it, but to recommend a drug
22 for a phenomenon that we don't even know why it's

1 occurring. We don't know that there's an immune-
2 mediated component to this. To recommend steroids,
3 I think, is very dangerous.

4 DR. WILSON: To follow up on that, could you
5 make a comment also about platelet replacement
6 since that's close to your heart as well, so under
7 which conditions my patients receive platelet
8 transfusions.

9 DR. ORTEL: So platelet transfusions
10 definitely needs hematology input or otherwise what
11 you really use platelet transfusions for is mainly
12 for bleeding manifestations, not for just a number.
13 So I would be cautious about recommending any kind
14 of transfusion cutoffs for the number alone, but if
15 the patient comes in bleeding, then platelets are a
16 reasonable alternative to use.

17 DR. WILSON: Other comments? Dr. Stroncek?

18 DR. STRONCEK: Yes. To your point, I think
19 it should be pointed out that the algorithms are
20 reasonable based on the data, but the data is
21 really very limited. And then I think the
22 recommendations are good ones to make the drug as

1 safe as possible, but they really don't ensure the
2 safe use of the drug.

3 I mean, they minimize the risk, but they
4 don't ensure the safety.

5 DR. WILSON: Dr. Kane?

6 DR. KANE: I was going to say, I think that
7 the weight-based algorithm is applicable in the
8 overall population. Considering all the different
9 forms of thrombocytopenia, I was not confident that
10 it would in and of itself enable us to escape the
11 sporadic and severe thrombocytopenia.

12 DR. WILSON: Others? Dr. Morrato?

13 DR. MORRATO: My comment relates to how you
14 convert this into labeling and thinking about it
15 as, once it's in label, it becomes very set. And I
16 think that the available evidence is kind of scant.

17 I was compelled by the FDA's analysis that
18 countered the company's. And I'm sure there's a
19 lot more information that we'll learn once it's on
20 the market. So I don't know if there's an in-
21 between zone as opposed to saying this is the
22 dosing regimen in the label versus a guidance that

1 could be adaptive over time as things are learned.

2 I'm not convinced the data we've been
3 presented kind of meets that standard of labeled
4 dosing.

5 DR. WILSON: Dr. Neaton, did you have a
6 comment?

7 (No response.)

8 DR. WILSON: No. Anybody else?

9 (No response.)

10 DR. WILSON: So I'm going to summarize this.
11 The question under discussion is dosing of
12 volanesorsen and the patient's weight. Especially
13 our pharmacologist and hematologist says that this
14 makes sense, this is what is commonly used for
15 other platelet disorders. And our hematology
16 experts voiced concerns about steroid use for
17 patients with low platelet counts, also about any
18 transfusions for patients without bleeding, and for
19 patients also I think the summary from them was as
20 well individuals with low counts should have a
21 hematology consult for the best advice on how to
22 move forward.

1 Then it was reiterated that we can minimize
2 risk, but we still have to translate this into safe
3 practice. So we're ready to go, I think. Now, we
4 have a comment, I think, from the FDA. Dr.
5 LaCivita, is this the right time for you?

6 DR. LaCIVITA: Yes, this would be.

7 DR. WILSON: Thank you.

8 DR. LaCIVITA: So I'd like to pull up if
9 it's okay sponsor slide CO-82. I don't have
10 access. Okay. So the next question; I don't want
11 to steal your thunder, but the next question is
12 regarding the REMS and I just wanted to make sure
13 that, for transparency, the advisory committee knew
14 what they were voting on.

15 DR. WILSON: Could you have the mic a little
16 closer so we can hear you a little better?

17 DR. LaCIVITA: Sure. So I wanted to make
18 sure that you understood that the REMS that is
19 being presented by the FDA does not include adult
20 patients confirmed of the diagnosis of FCS. It
21 really includes prescriber certification, pharmacy
22 certification.

1 The documentation of the safe-use condition
2 would be the patient-provider agreement form, so
3 they're informed of the risks before they start
4 treatment. The monitoring is not a blood draw
5 that's done before the patient gets the dose. It
6 is a status form that we would follow up with every
7 90 days.

8 So I just wanted to make sure that point of
9 clarification was clear and the things to the
10 right, where the sponsors included the laboratory
11 analysis, the patient blood draw are not part of
12 the REMS. They are voluntary things proposed by
13 the sponsor. Thank you.

14 DR. RAUFMAN: Can I ask a question?

15 DR. WILSON: Yes. Let's get this clear.
16 This is an important issue. Yes, go ahead.

17 DR. RAUFMAN: Does it require that the
18 patient have had an episode of pancreatitis?

19 DR. LaCIVITA: The proposal does not include
20 that.

21 DR. WILSON: Yes. So Dr. Morrato, I want to
22 spend a minute or two on this because we're going

1 to discuss it, but let's make sure we're clear on
2 what we're discussing. Dr. Morrato?

3 DR. MORRATO: So two clarifying questions,
4 because we had a question over here about, does
5 this preclude pediatric use if they're not verified
6 age or can you use it off label?

7 DR. LaCIVITA: The FDA's proposal really
8 focuses on the risk and it does not at this point
9 in time. But we'd like to hear the committee's
10 thoughts on that.

11 DR. MORRATO: Then the second piece was, if
12 I'm understanding, every 90 days, someone is giving
13 FDA or this system a status. And in that status
14 report would be their platelet count.

15 DR. LaCIVITA: Collecting information about
16 their platelet count, maybe a bleed, things like
17 that.

18 DR. MORRATO: So it could be 1 test in
19 90 days, not every --

20 DR. LaCIVITA: There could be multiple
21 tests.

22 DR. MORRATO: Right. So what would happen

1 if we all agreed that every two weeks is the right
2 thing to do and they are not doing that? What
3 would the system feed back? You have one platelet
4 count, so something's happening. So what would the
5 REMS do in that situation?

6 DR. LaCIVITA: The status form would collect
7 information with regard to a platelet nadir and
8 maybe specific adverse events that were happening
9 regarding that.

10 DR. MORRATO: So what's the feedback loop to
11 the patient or the doctor as it relates to
12 prescribing, anything or dispensing?

13 DR. LaCIVITA: Because the management of
14 these patients is complex that will be under
15 medical care.

16 DR. MORRATO: Then the last one is around
17 informed consent up front. I think I heard that.

18 DR. LaCIVITA: Yes, so the patient
19 understands the risks and they're aware of the need
20 to have the monitoring performed.

21 DR. MORRATO: Yes. So since this is a
22 lifelong drug, would there be a re-assenting kind

1 of process built in over time as there's new
2 information that comes out in a prospective way.
3 It's not like, I've been taking this for 10 years,
4 I'm going to really read this new med guide thing.

5 How do we help ensure patients are staying
6 up to date and re-attesting that it's still the
7 right thing for them?

8 DR. LaCIVITA: Those are considerations that
9 we could build into the REMS, but certainly your
10 thoughts on that would be helpful.

11 DR. WILSON: As a follow-up, would you like
12 us to discuss elements of some of these boxes,
13 these decision boxes, or no, just the general
14 concept, general concept?

15 (No response.)

16 DR. WILSON: So we're now going to go to
17 question 5, discussion point 5. We're skipping 4.
18 We may come back to that, but we're going to go 5
19 and then a voting question. And then we're also
20 skipping 6 and 6 will come maybe later, so let's
21 just stay with the numbering that we were just
22 recently given at the break. We're going to go to

1 5 and then we're going to go to the vote. Okay?

2 So number 5, discuss whether a risk
3 evaluation and mitigation strategy, is necessary
4 and would be able to ensure that the benefits of
5 volanesorsen outweigh the potential risk of serious
6 bleeding due to severe thrombocytopenia.

7 If volanesorsen were to be approved want to
8 a REMS, discuss whether you would recommend any
9 changes to the REMS presented by FDA.

10 Can I ask a question, FDA? Don't we have a
11 slide on that? We certainly had it in an advance
12 packet for the REMS by the FDA. Is there a slide?
13 Perhaps we can open the discussion and they can
14 find that.

15 I'm not sure it's that critical, but you
16 refer to it in the discussion point.

17 DR. LaCIVITA: Go to Dr. Chapman's
18 presentation and it was slide 13. Is that helpful
19 or do you need more details?

20 DR. WILSON: If that's what you want us to
21 leave up, let's leave that up. Okay? All right.
22 So we're to discuss. This is what the FDA is

1 recommending, and whether a risk evaluation and
2 mitigation strategy is necessary and would help to
3 assure the benefits of volanesorsen outweigh the
4 potential risks. That's the question.

5 Dr. Everett, clarifying?

6 DR. EVERETT: Just a quick clarifying
7 question; a REMS registry -- I think what we're in
8 part maybe interested in is the ascertainment of
9 adverse events in an unblinded fashion in this
10 population as they would move forward.

11 Is that the REMS registry or is that what
12 the sponsor presented as a registry for all
13 patients who would be on this drug?

14 DR. LaCIVITA: I can only speak for these
15 two.

16 DR. EVERETT: Yes. The question is
17 specifically about REMS registry.

18 DR. SHARRETT: So the REMS registry would
19 be each patient would be enrolled in the registry
20 for the REMS. And that would collect patient
21 information regarding information to help us better
22 mitigate this risk. It wouldn't be, like, every

1 platelet count. It would be information basically
2 from the status form.

3 DR. EVERETT: So if there was an adverse
4 event, presumably that would show up on the status
5 form and then would be collected as part of the
6 REMS registry?

7 DR. LaCIVITA: Correct. That would be the
8 assumption. Thank you.

9 DR. WILSON: Dr. Neaton?

10 DR. NEATON: So all these forms come in.
11 Who's responsible for summarizing them on a regular
12 basis? I'm looking at the data.

13 DR. LaCIVITA: The sponsor.

14 DR. NEATON: That will be something that
15 would be required as part of the program?

16 DR. WILSON: Ms. McCollister?

17 MS. MCCOLLISTER-SLIPP: I'm guessing that
18 there will be off-label use of this medication. I
19 mean, I know, if I had a kid that was 14 and they
20 were having lots of pancreatitis, I'd probably be
21 inclined to try to get them on the medication if
22 there weren't any other options.

1 But I mean, how does the REMS strategy as
2 currently outlined deal with those issues? Is the
3 off-label use going to be collected as part of the
4 registry?

5 DR. LaCIVITA: The patient enrollment will
6 probably collect information with regard to the
7 patient's age, but the REMS strategy is really to
8 mitigate the risk. It's not specific for off-label
9 use.

10 MS. MCCOLLISTER-SLIPP: It won't preclude
11 off-label use?

12 DR. SMITH: Yes. I think that's fair. I
13 think the way that we've discussed it, envisioned
14 it, and based on some past experience, I would not
15 count on the REMS to be a tool to prevent off-label
16 use. We wouldn't be looking for that use.

17 MS. MCCOLLISTER-SLIPP: But the registry
18 would collect data from off-label use, so we would
19 be getting data.

20 DR. LaCIVITA: So the registry would collect
21 information on each patient that is receiving the
22 drug.

1 DR. WILSON: Dr. Sinclair as well?

2 DR. SINCLAIR: I would say that, yes, a REMS
3 is necessary. And I noticed from the sponsor's
4 slide that the first prescription is tied to a
5 platelet count, but then it gets a little unclear
6 whether it's a monthly prescription or a 90-day
7 prescription. I think they said monthly.

8 So anyway, I think it's important to keep an
9 eye on the platelet count and hold the prescription
10 if it's not where it needs to be in some way.

11 Also, about the registry, I would encourage
12 consideration that you enroll a non-treated
13 comparison group to shine some light on the type 2
14 thrombocytopenia. It's hard to interpret the
15 results if you don't have a comparison group in a
16 perfect situation.

17 People may go off, you could enroll them,
18 and you can also try to understand the natural
19 history of the disease better that way. People
20 could become pregnant and that should be captured
21 in a separate module. Personally, I would like to
22 see it be restricted to the REMS. I liked the

1 adult patient part of the REMS. I don't feel
2 comfortable with children being given the
3 medication until they're evaluated.

4 That's all. Thank you.

5 DR. WILSON: Others? Dr. Raufman?

6 DR. RAUFMAN: Yes. I'm confused, but it's
7 not the first time. I'm confused between what's up
8 on that slide and what the sponsor is proposing
9 because, if we go along with what the sponsor is
10 proposing, it seems to limit off-label use because
11 they're saying they're not going to ship drug
12 unless a number of stipulations are met, including
13 that it's an adult patient, confirmed diagnosis of
14 FCS.

15 So that seems to me to limit off-label use.
16 I would also add that I understand that the first
17 episode of pancreatitis could be highly morbid,
18 could even be lethal. But if there's a high risk
19 to the drug, I'd rather it go to a high-risk
20 population. And it seems to me that people who
21 have had a previous episode of pancreatitis would
22 represent a higher-risk population.

1 So I would include that in not only FCS, an
2 adult with FCS, but an adult with FCS who's had an
3 episode of acute pancreatitis. But I like their
4 decision tree a whole lot better. It's just more
5 detailed than what's up there.

6 DR. WILSON: So as I understand what
7 Professor Raufman just said, he would consider
8 especially including a history of pancreatitis as
9 part of the study population, would be included in
10 REMS.

11 You're getting close to our voting
12 questions. Let's try to confine ourselves to the
13 actual REMS principles, which is what the FDA
14 wants.

15 DR. YANOVSKI: Yes. I want a clarification,
16 too, because it sounds like what the sponsor had
17 proposed was much more structured than the REMS
18 that the FDA is putting out there, because that
19 included again limitations as to which types of
20 patients they would ship it to, routine platelet
21 monitoring, whereas the REMS that I see here could
22 be open to off-label use, which would mean you'd

1 get a broader population of points, maybe on other
2 kinds of medications.

3 You wouldn't necessarily be getting as
4 routine monitoring as the sponsor originally
5 proposed. Am I correct about that?

6 DR. WILSON: Yes. Please identify yourself
7 and speak.

8 DR. PIPPINS: My name is Dr. Pippins. I'm
9 the deputy director for safety for the Division of
10 Metabolism and Endocrinology Products. Could we
11 please bring up Dr. Chapman's slide 15? So I want
12 to remind the committee that we presented the REMS
13 as currently envisioned by the FDA. The applicant
14 has proposed additional activities in the form of a
15 patient support program.

16 As has been noted, those additional
17 activities are outside of the REMS and are not
18 something that is accessible nor enforceable to FDA
19 and that really pertains to our authorities under
20 the law.

21 I want to highlight this slide, which talks
22 about the REMS capabilities and the REMS

1 limitations. There's been some discussion, for
2 example, about the issue of off-label use. And
3 certainly, the committee in their voting discussion
4 can talk about what they envisioned as being
5 potentially an appropriate patient population,
6 appropriate indication for this product.

7 But what I want to highlight here is, under
8 the capabilities, we're talking predominantly about
9 education of prescribers. We're talking about
10 making patients aware. We are talking about
11 collecting some additional data that might inform
12 the safety risk moving forward into the future.

13 What we are not citing as something that the
14 REMS will accomplish, what the REMS will not
15 accomplish -- it cannot enforce monitoring as
16 currently described in the prescribing information.
17 That is not something that the REMS, as envisioned,
18 can accomplish.

19 While the REMS can communicate what would be
20 an appropriate patient population for prescribers,
21 the REMS itself does not necessarily enforce on- or
22 off-label use.

1 DR. WILSON: Is that helpful, Dr. Yanovski?

2 DR. SMITH: I'll just piggyback on
3 one -- this is Jim Smith -- of the considerations
4 regarding the off-label question. As you've heard
5 this morning, there are probably a variety of
6 opinions of how one would even make the diagnosis
7 of FCS.

8 So one could envision an attestation that
9 this patient has FCS. That could be interpreted
10 many different ways by many different clinicians
11 and I would leave it to you to consider how helpful
12 in the end that would be.

13 DR. WILSON: Yes, Dr. Morrato?

14 DR. MORRATO: Yes, quick question then. So
15 I know there are programs that are no blood, no
16 drug, and those fall within REMS. I think I just
17 understood that those aren't provisions. Is it
18 because things are changing as to FDA's authority
19 in this case or is it more or less your assessment
20 of what seems the right appropriate burden, et
21 cetera; given the situation, this is what you're
22 recommending.

1 DR. LaCIVITA: We were trying to balance the
2 safety with the burden here and it wasn't clear to
3 us whether the additional requirements which ensure
4 a greater degree of safety based on the complexity
5 of trying to treat these patients.

6 DR. MORRATO: So that seems appropriate.
7 Just since I asked the question, I'll just close
8 the loop. I think, again, in the area of informing
9 and knowing that patients are going to be on this
10 potentially lifelong mechanism of updating that
11 information or attestation and it's not like, once
12 I started, that's the last time I get that
13 information would be, I think, useful to build into.

14 DR. WILSON: Any further comments? Can I
15 try to summarize? So this was a question of
16 discussing the appropriateness of REMS. I did not
17 hear any negative opinions. The first speaker,
18 Dr. Sinclair, felt very strongly the REMS was
19 necessary and most of the content was very
20 supportive of needing REMS, but we have two
21 versions put before us in our reading materials and
22 in our presentations.

1 So there are principles, but there's also a
2 little bit of uncertainty exactly what REMS might
3 be because that's not fixed at this point and would
4 be determined going forward.

5 There was felt very strongly a need in a
6 REMS program to monitor, but we were reminded,
7 especially by FDA, that the FDA is not in a
8 position to, quote, "follow through" for, quote,
9 "enforcement of that." There was especially a
10 leaning towards use of these medications in adults
11 and we've see no information in adolescent and
12 pediatric groups.

13 It's not clear whether they would be
14 included going forward and/or what might happen for
15 outside of usual use, but for compassionate use and
16 off-label use.

17 Let's see. There has been some interest
18 especially in targeting perhaps individuals with a
19 history of pancreatitis for future investigation
20 and use because one of the secondary aims in the
21 current study was the prevention of pancreatitis
22 and it's been underpowered up until now to address

1 this issue.

2 I think that's most of the issues. One was,
3 we were reminded by the FDA that a REMS is largely
4 an informational program. It does not enforce a
5 program and it's a monitoring program. I still
6 don't have resolved in my mind -- Dr. Morrato
7 brought up the concept of no blood, no drug,
8 meaning if you didn't get tested, that's something
9 that would be decided by the providers and the care
10 system.

11 It sounds like REMS would not be monitoring
12 that, that FDA would be collecting data on that,
13 but would be not quote, "enforcing" the no blood,
14 no drug policy. Cynthia LaCivita, any further
15 clarification?

16 DR. LaCIVITA: Just a point of
17 clarification.

18 DR. WILSON: Yes.

19 DR. LaCIVITA: The FDA does have the
20 authority to require monitoring prior to
21 dispensing. The proposal that we have set forth is
22 in the form of a status form, so that would be a

1 requirement they would need to submit that form
2 every 90 days to provide that information.

3 What is not part of the REMS is the patient
4 support program that the sponsor has suggested.
5 It's a voluntary program where they're going to do
6 home visits and other things to help facilitate
7 obtaining platelet counts.

8 So that is a voluntary program that's being
9 proposed by the sponsor outside of the REMS, so
10 just a point of clarification.

11 DR. WILSON: Thank you very much. That's
12 very helpful. I think we're ready to move forward.
13 Now, we have 10 minutes left before the hour.
14 We're going to vote as our next step, question 7.
15 I'm going to read the question.

16 What's going to happen is, each person is
17 going to vote and we vote simultaneously. So I'm
18 going to give you the introduction to the voting
19 system and then we're going to go.

20 So we will be using an electronic voting
21 system for this meeting. Once we begin the vote,
22 the buttons will start flashing and they will

1 continue to flash even after you have entered your
2 vote.

3 Please press the button firmly that
4 corresponds to your vote. If you are unsure of
5 your vote or you wish to change your vote, you may
6 press the corresponding button until the vote is
7 closed. After everyone has completed their vote,
8 the vote will be locked in.

9 The vote will then be displayed on the
10 screen. And Commander Bonner will read the vote
11 from the screen into the record. Next, we will go
12 around the room and each individual who voted will
13 state his or her name and also how they voted and
14 that will go into the permanent record.

15 You can also state the reason why you voted
16 as you did if you want. We will continue in the
17 same manner until all questions have been answered
18 and it's really limited here, so we're not going to
19 have lots of questions, but we have two parts of
20 this.

21 We actually have only one voting question,
22 though. Does that make that clear? So I'm going

1 to read, as you can see here at the top, the whole
2 thing. Based on the information included in the
3 briefing materials and what was presented today,
4 has the applicant provided sufficient efficacy and
5 safety data to support approval of volanesorsen?

6 If yes, provide your rationale and any
7 recommendations regarding the indicated patient
8 population, dosing, clinical monitoring, risk
9 management strategies, and/or post-marketing
10 studies. If no, provide your rationale and comment
11 on what additional data would be required to
12 support approval.

13 Anything further before? Any questions? So
14 your buttons are flashing. You all have a chance
15 to vote. And remember the comments as we go around
16 the room are going to be more important than you
17 might guess because it really helps frame what goes
18 forward from this meeting onward.

19 (Voting.)

20 DR. BONNER: For the record, for yes, 12,
21 for no, 8, 0 abstained.

22 DR. WILSON: It's hard to read, but what

1 we're going to do next is, for those who voted,
2 we're going to go around the room. We're going to
3 start over to my right, which I can't read all the
4 names there. I'm sorry.

5 Meghan, you're going to start off, and then
6 Dr. Kane, and then Dr. Raufman, and we'll go in
7 that direction all around. So you're going to
8 start your name, how you voted, and if you would
9 like to supply a rationale for how you voted, that
10 would be helpful.

11 DR. ROWCLIFFE: Sure.

12 DR. WILSON: State your name first to start
13 out.

14 DR. ROWCLIFFE: Sure. So I'm Meghan
15 Rowcliffe. I voted yes. I think that there was
16 robust data to indicate that this drug is
17 effective. And I think that, if appropriately
18 monitored with the REMS that we've discussed, it
19 could be very beneficial to patients with this rare
20 form of disease. Thank you.

21 DR. WILSON: Yes?

22 DR. SMITH: Dr. Wilson? Jim Smith. If I

1 could remind folks, especially since we skipped
2 question 4, if you have any recommendations about
3 the indicated population that are different than
4 just familial chylomicronemia syndrome, this would
5 be the time to include that in your statement, just
6 since we skipped that discussion point. Thanks.

7 DR. WILSON: Yes. So next, let's proceed.
8 Dr. Kane?

9 DR. KANE: I voted no and, thinking about
10 it, if the population studied was comprised of the
11 patients who presented to us at 1:00, I think this
12 might have been a much easier discussion to have.

13 I had difficulty in extrapolating from the
14 reduction in triglyceride to a clinical benefit.
15 No question of reduction in triglyceride, but
16 that's the part that I'm certain about. The unmet,
17 I'm not so certain.

18 I almost don't understand the difference in
19 the experience as we heard at 1:00 versus what was
20 documented in the trial. The second problem I have
21 is that the population that we know about at this
22 point is still susceptible to a substantial risk of

1 severe thrombocytopenia.

2 While the REMS may help us, I do not know
3 yet from the basis of any information that I can
4 rely on the REMS that will create the safety that
5 we need to. Thank you. And unfortunately, that's
6 my ride to the airport.

7 DR. WILSON: Yes. We may excuse you,
8 Dr. Kane. Thank you very much for your
9 participation. Go ahead next, Dr. Raufman.

10 DR. RAUFMAN: Jean-Pierre Raufman. I voted
11 yes, primarily for two reasons. I think, one, the
12 sponsor provided compelling evidence that the drug
13 lowers triglyceride levels substantially and I was
14 swayed by the comments at the open session. I
15 think that there is clearly a group of patients
16 with this disease that would benefit highly from
17 this agent. And based on that, I would recommend
18 that the indicated patient population be more
19 clearly defined as people with this disorder and
20 the criteria for this disorder, there could be some
21 definition of this disorder that doesn't require
22 genetic testing necessarily.

1 There could be a threshold for triglyceride
2 levels. There are experts in this field. We heard
3 from several who I'm sure you could come up with a
4 paragraph of a definition. And again, based on the
5 fact that risk is relative, I think it's reasonable
6 to limit use to people who meet the criteria for
7 the condition and have had at least one episode of
8 acute pancreatitis.

9 I'm not so sure about kids. I mean, there
10 are kids who can have a very aggressive form of
11 this disease and I wouldn't limit their access
12 necessarily to this agent. I would put in a bunch
13 of caveats, and safety features, and so on, but I
14 wouldn't deny them treatment if they've got awful
15 disease.

16 DR. YANOVSKI: Hi, Sue Yanovski. I voted
17 no. And I did this feeling rather conflicted
18 because I'm very cognizant that this is a rare,
19 serious, and debilitating disease without other
20 effective treatments.

21 I really want to see an effective treatment
22 available and there's no question that volanesorsen

1 is effective in dramatically reducing
2 triglycerides. However, I had a lot of concerns
3 about whether the data presented by the sponsor
4 actually established a favorable risk-benefit
5 ratio.

6 I was concerned about the large number of
7 dropouts, that people had a dropout because of SAEs
8 or lack of tolerability and lack of data on the
9 dosage regimen that they've actually proposed. I
10 also wish we could have seen some sort of
11 improvements in patient-reported outcomes like pain
12 or quality of life.

13 Finally, I'm concerned with the REMS. I'm
14 concerned that, once this is on the market, we're
15 going to see a lot more off-label use and in
16 patients in whom it wasn't tested. And I don't
17 really know how to prevent that once it's on the
18 market.

19 I'd really like to see further data using
20 the proposed dosing. I'd like to see more safety
21 data and I'd like to see more data on clinical and
22 patient-reported outcomes.

1 DR. ORTEL: Tom Ortel. I voted yes. I
2 voted what I considered to be probably a qualified
3 yes. I do think it is important that we establish
4 the diagnostic criteria for who should be getting
5 the drug. In hematology, we're using next-gen
6 sequencing more and more to characterize rare
7 diseases.

8 I think that actually looking into having
9 that as a requirement is not an unreasonable step.
10 I think that there needs to be some better
11 clarification in the REMS between what the sponsor
12 is putting together, what the FDA is putting
13 together to clarify some things and some of the
14 other concerns I had about treatment
15 recommendations, I think, need to be addressed.

16 But as far as lowering the triglycerides and
17 the impassioned statements at 1:00, I think that
18 that's why I voted a qualified yes. And I have to
19 get to the airport, too.

20 DR. SHAMBUREK: I'm Robert Shamburek and I
21 voted yes. I must first commend the applicants,
22 both of them, for pursuing a rare lipid orphan

1 disorder which is frequently neglected.

2 Enrolling 66 patients in an orphan disorder
3 is very impressive. Volanesorsen impressively
4 lowered triglyceride in familial chylomicronemia
5 syndrome in a very desperate unmet need for these
6 patients. The levels of triglyceride below 750 to
7 1,000 should offer significant improvement in
8 clinical events in the orphan disorder.

9 I believe there will be benefit for
10 pancreatitis and other clinical symptoms, but I
11 don't think the CS6 pivotal was powered in order
12 and also had lower-risk patients that wouldn't show
13 up in 1 year.

14 With that said, there are safety issues of
15 platelets and bleeding that are a major concern.
16 We've heard there's predictable and
17 underpredictable ways of following this.

18 If the risk is deemed significant by either
19 the FDA or the physician, there may be a need for
20 more stringent criteria such as the need for
21 recurrent pancreatitis, noting that one episode can
22 be fatal, but we have to do the risk-benefit.

1 I think the dosing recommendations for what
2 we know now, which has been stated as very limited,
3 is what we'd have to propose. The REMS follow-up
4 is very important. Risk management strategies
5 should certainly include the platelet, immunologic,
6 and bleeding issues. The post-marketing should
7 focus on the platelet, bleeding, and pancreatitis
8 events.

9 I think there is a need to get this into
10 kids somehow, but there still remains a major issue
11 of, I think, for safety with weight and dosing that
12 are lacking and I don't think can be extrapolated.

13 So I voted yes, that patients should be
14 informed of the current unpredictability of
15 platelets and bleeding risk, and know there is the
16 REMS to help us out and weigh that against the
17 unpredictable pancreatitis risk.

18 MS. CUARESMA: Nichole Cuaresma. I voted
19 yes. I wish I could just say what he said and you
20 can put that on record because it's going to sound
21 better than what I'm going to say, but it's very
22 similar in that this orphan drug is obviously

1 limited to a very rare population, two of which
2 live in my home.

3 So the primary endpoint was to reduce the
4 triglyceride level, which it did, and I think the
5 risk versus benefit is going to be different for
6 each patient. And again, I'm not a medical
7 professional, but the mutations in one of my family
8 members is different, a little different than the
9 other.

10 One is very extreme and needs this ASAP and
11 the other maybe won't. So I think each case is
12 going to be different and even more rare than the
13 other in some cases. And I think it's up for the
14 patient and the adults decide on whether or not
15 they want to take this medication in the end.

16 So the close monitoring, I definitely agree
17 with, and the REMS. In fact, I liked the more
18 detailed monitoring that the sponsor had put up.
19 And the two-week blood draws, I think, is
20 important, although I will say that, for pediatric
21 use -- and I do have a two-year-old and I know
22 there's not very many infant patients that are

1 recognized in the United States at this point, but
2 I don't quite feel comfortable with where this is
3 at right now for pediatric use.

4 But again, in an adult, I would say that I
5 would agree continuing or the orphan drug as it
6 stands. Thank you.

7 MS. McCOLLISTER-SLIPP: This is Anna
8 McCollister-Slipp. I voted yes. And there are
9 lots of things with the data that was presented
10 that I didn't think were where I would like to see
11 it. It's an incredibly small population.

12 I know designing studies for rare disease
13 can be very difficult in terms of both powering,
14 recruitment, retention, et cetera. And I think
15 there's a lot of data that's missing. I'm
16 intrigued by the fact that we got a decrease in the
17 biomarker, which is important and apparently
18 clinically significant, but we didn't see any
19 changes in pain and the numbers of pancreatitis as
20 me as a patient, if I were faced with it, would be
21 sufficiently convincing, but they weren't
22 brilliant.

1 So having said that, as a patient who takes
2 16 different medications, 3 of which had a really
3 hard time getting approved and making it through
4 advisory committees, I'm a big believer in the
5 perfect, particularly perfect dataset not being the
6 enemy of the good and the clinically helpful.

7 I think that patients who live with a
8 debilitating long-term disease could get really
9 smart on that and, if they're working with their
10 physicians -- and I think most people who live with
11 that kind of a condition would be - they get pretty
12 good at evaluating the risk-benefits.

13 If the drug doesn't work, if the benefits
14 don't outweigh the risks and the burden, they won't
15 take it. So I think we should be collecting lots
16 of data and figuring out which populations are
17 best, so that we can have better guidance for
18 physicians and clinicians and patients moving
19 forward.

20 In terms of the REMS strategy, I think it's
21 absolutely critical. You have to have education.
22 I mean, monitoring seems to be really important.

1 And I would just caution that the least burdensome,
2 the least restrictive you can be, the better just
3 because those kinds of things have a way of getting
4 calcified through the insurance system, which can
5 create significant burdens on patient and can
6 create significant barriers to access.

7 What that would mean in this particular
8 case, I don't know, but I have to live with that
9 with at least one of the medications I take. And
10 in terms of ways to do that, there are some really
11 clever uses in digital health, consent forms where
12 you have quiz-based consent.

13 I really like the idea of reconsenting just
14 to make sure that people continually stay aware of
15 the risks and make sure that the risks are top of
16 mind, not in a way that's burdensome or obnoxious,
17 but there's some good models out there that you
18 could look at.

19 DR. BURMAN: Ken Burman. I voted yes. It
20 is always difficult to balance the risk of disease
21 versus the risk of the particular medication. This
22 balance is especially difficult in orphan diseases,

1 where we have to compromise our desire for an
2 optimal study with real-life issues, such as for
3 example the number of patients that can be
4 recruited in a study and how long they can be
5 studied and analyzed long term.

6 The central point to me is this disease is
7 caused by an elevated triglyceride and the sponsor
8 definitely showed that the agent was successful in
9 lowering triglyceride s that I would expect all the
10 other sequelae that may be related to elevated
11 triglyceride to be abrogated with the medication.

12 I'd also like to commend the sponsor and the
13 FDA for their presentations, which were excellent.
14 I strongly believe in the REMS study that was
15 mentioned, the more detailed one.

16 I have strong views that I think that the
17 FCS definition is a little vague, although genetics
18 doesn't prove that everyone has it. I think
19 genetics analysis should be initiated in every
20 patient and, if it turns out to be negative, then
21 strong clinical judgment in addition.

22 I raised the issue of a post-marketing study

1 that would look at many of the issues we've
2 discussed today with regard to different dosing and
3 quality of life issues. And I also commend the
4 open session speakers for their impassioned
5 comments.

6 DR. MORRATO: Elaine Morrato. And I also
7 voted yes in favor. Clearly, there's a strong
8 unmet need for a rare genetic condition with great
9 suffering as we heard, significant physical,
10 emotional, and financial burden of the disease.

11 It came down to me -- I think we were being
12 asked to trade off two potentially life-threatening
13 conditions, the pancreatitis as well as the drug-
14 attributable thrombocytopenia. Unfortunately, we
15 had limited information on both of them.

16 But I think, at the end of the day, I felt
17 that, for some patients, the trade-off to avoid the
18 pancreatitis risk made sense given their personal
19 history. But recognizing that, for others, that
20 may not make appropriate benefit-risk for them.

21 So I ended up erring on the philosophy in
22 this particular situation, following more of a

1 compassionate use kind of program and the desire to
2 support patients to make informed decisions.

3 Having said that, though, I think patients
4 should be aware there's a 1 in 10 risk, 9, 10
5 percent of the patients fell below 50,000, a 1 in
6 20 risk of below 25. And so sometimes, in our
7 enthusiasm of hearing the promise of the efficacy,
8 we don't always hear the downside risks as well.

9 So I really want to make sure that the REMS
10 program is rigorous and strict in that regard, that
11 there's appropriate informed consent. I think it
12 still wasn't so clear to me the regulatory teeth on
13 the 90-day status form. I think there needs to be
14 some consequences tied with dispensing to make sure
15 that system doesn't get out of control.

16 In terms of the frequency of reporting, I
17 know REMS can set the standard of reporting
18 timeliness. I would expect it to initially be
19 quarterly as opposed to on a longer time frame.
20 And I think patients as well as providers need to
21 know going in that the monitoring itself is not
22 necessarily going to mitigate the risk.

1 I see greater value in its pharmacovigilance
2 and understanding of the risk profile value as
3 opposed to it is a strong risk mitigation in
4 itself. But at the end of the day, I believe that,
5 in real-world prescribing with a strict REMS like
6 this, as we've seen in other programs, it will be
7 self-limiting to which centers or clinicians and
8 patients, particularly the centers and clinicians
9 that will actually sign up for this, we already
10 know.

11 With a few hundred Americans having this
12 condition, it's already being concentrated among a
13 few providers that treat. So I think, at the end
14 of the day, largely the centers that were doing the
15 trials will probably be the centers providing care.
16 But a last comment I wanted to include is that I am
17 concerned of the cost of this. We don't talk about
18 cost here.

19 But to patients, we heard from some in the
20 open forum how the disease has bankrupted their
21 families, but we're also hearing more and more in
22 the news about narrowly targeted drugs that charge

1 hundreds of thousands, if not millions of dollars a
2 year.

3 I'd hate to see a trade-off of where it's
4 saving costs in one area only to be adding costs in
5 another area.

6 DR. BUDNITZ: Dan Budnitz. I voted yes for
7 approval, but if there were another treatment
8 option for FCS, I probably would not have voted yes
9 based on the trial data that were presented.

10 I think I want to make three points. One
11 is, as folks have mentioned, the efficacy and
12 safety data are extremely limited, a few patients
13 in relatively short follow-up for a lifelong
14 period. I'm also concerned about the unknown
15 mechanism or mechanisms of thrombocytopenia and I
16 do worry that, over the course of lifelong therapy,
17 more patients are likely to experience
18 thrombocytopenia than events of pancreatitis
19 avoided.

20 But it's hard to gauge the relative value
21 from each of those conditions. I did note some
22 concern over the potential signal, anaphylaxis, and

1 serum sickness. That was brought up. But I think
2 the only way to understand that better is with more
3 data.

4 One other point about the safety data that
5 was submitted, I think, really was -- the analysis
6 was compromised by the high dropout rate. I
7 mentioned that before, but I agree with the FDA
8 reviewer that, the measure of efficacy is probably
9 biased due to the high rate of treatment
10 discontinuation, but I think that also applies to
11 the adverse event rates as well and, in particular,
12 when essentially there's no dropouts of the placebo
13 group but very high rates for the treatment group,
14 it's kind of like an incidence density for adverse
15 drug events, would be a useful measure to include
16 in the future.

17 Then finally, I do appreciate the sponsor's
18 stated commitment to have their risk mitigation
19 program. I think that is critical to have that
20 centralized coordination, and laboratory testing,
21 and reporting to clinicians before dispensing,
22 because I do think that this is really the only way

1 we'll get more information about the efficacy,
2 effectiveness, and adverse events.

3 One thing that could be done is enrollment.
4 While there may be some debate of definition of FCS
5 when enrolled, documentation of clinical symptoms,
6 triglyceride level despite adherence to low-fat
7 diet, failure of other therapies, and history of
8 pancreatitis, abdominal pain documented, that would
9 be helpful.

10 Finally, the logic behind biweekly platelet
11 testing may be lacking, but it seems like the
12 reasonable approach again to limit the time that
13 patients might be idiosyncratically
14 thrombocytopenic while taking other medications.

15 DR. WILSON: Peter Wilson. I'm supposed to
16 vote next, but Dr. Epstein has to go, so he's going
17 to tell us how he voted and then come back to me.

18 DR. EPSTEIN: My apologies. I have an
19 emergency. Someone swallowed a box of razor
20 blades. So I voted no even hearing the passion of
21 the people with FCS, because there's always a risk-
22 benefit ratio and, really, here I believe we're

1 trading one disease for another in a population
2 that wasn't studied for the condition for which we
3 say that we're going to help.

4 We didn't show clinical benefit, but we
5 showed a serious adverse event, which is yet
6 another new clinical disease. And in my
7 experience, we've had drugs before that have
8 created new clinical problems that, in my
9 experience with previous committees, have been
10 withdrawn for much, much less numbers of adverse
11 events into the 1 in 1,000.

12 But here, we have something that's causing a
13 new disease, thrombocytopenia. There's also the
14 serum sickness, the anaphylactic shock, these very
15 high rate of injection site reactions which need to
16 be addressed, maybe with the formulation.

17 There's still questions about the dosing,
18 the dosing intervals, the monitoring. And then
19 there was the main thing I think which was the high
20 dropout, which I think makes it very difficult to
21 actually correctly analyze this data.

22 So all in all, I thought that it was a

1 yeoman's effort to get to this point, but it missed
2 the mark. And I apologize for leaving.

3 DR. WILSON: Thank you very much. You're
4 gone. Dr. Epstein had to leave. So Peter Wilson;
5 I voted yes. I'm not going to repeat the other
6 reasons that have been voiced before. I want to
7 make some suggestions to how we might move forward.
8 Number one is to collect more metabolic data for
9 people as people are being recruited into either
10 studies or registries, which means comprehensive
11 laboratory data and a laboratory database that will
12 be able to be explored multiple times as we go
13 forward for both proteomics and genomics because
14 we're going to potentially redefine this disease
15 each year or ever few years as we find more genetic
16 and other variants related to hypertriglyceridemia
17 and not only at the outset, but also for anybody
18 who experiences a serious adverse response,
19 especially for thrombocytopenia, also to collect
20 another specimen there and to have a special
21 registry database where molecular scientists can
22 investigate this.

1 So that's number one. Number two is, I
2 favor two post-marketing studies and one would be,
3 as has been mentioned before, is patients who have
4 already had pancreatitis and to see whether this
5 molecule prevents pancreatitis.

6 I believe we may have an estimate in the
7 range of 400, perhaps more than that, person-years
8 of exposure may help to address this question and,
9 with larger experience, we may be able to get an
10 answer, especially starting with people who have
11 already experienced pancreatitis once.

12 Then secondly, I think an area of special
13 concern is pediatrics, but especially when we get
14 into the adolescence, where they could consent
15 themselves and they may have already multiple
16 episodes of pancreatitis. It's to do a safety
17 study in, let's say, post-14-year-olds, because
18 some of these have had multiple episodes of
19 pancreatitis and have had molecular diagnosis at
20 that time.

21 That would move it forward and not just with
22 a registry, but with a post-marketing at least

1 safety study and perhaps outcomes study. So I'm
2 done.

3 DR. EVERETT: This is Brendan Everett. I
4 voted no. It's a qualified no. I think, to use
5 Dr. Yanovski's comment, it was a difficult no. And
6 I think a lot of us have applauded the sponsor for
7 their efforts in bringing the drug forward.

8 I want to add perhaps some less laudatory
9 comments in the sense that I think they also made
10 some critical missteps early in the development
11 program, for example in not choosing to move
12 forward with two doses instead of one or with
13 different dosing frequencies that would have
14 informed the decision that we made today and made
15 it much easier, A, to understand the risks, B, to
16 understand the benefits on the alternative dosing
17 regimen that they have proposed and C therefore
18 allowed me at least to potentially vote yes.

19 I think I'm satisfied that, with the dose,
20 A, there's a clear unmet medical need and we heard
21 that. And importantly, there's evidence that the
22 dose that was used in the study, albeit with

1 significant dropout, caused substantial reductions
2 in triglycerides.

3 I don't know what the proposed dosing
4 regimen will do either in terms of benefits or
5 risks and that's one of the key reasons for my vote
6 no.

7 I think, as I mentioned, there's an
8 important role for this medication in the right
9 population and that's really the source of my
10 hesitation in voting no, the people that we heard
11 from earlier, because even if there are people with
12 this condition who take the medication and find
13 that they can't tolerate it, there are other people
14 who find that they can.

15 For those patients, it offers significant
16 benefits clearly. I want to note that choosing who
17 those patients are is very difficult and this gets
18 to question 4. In particular, the study of 66
19 patients had 9 patients who were subsequently
20 identified to not have FCS by the study-specific
21 criteria that were used, so that's 14 percent of
22 patients enrolled in the clinical trial program.

1 That being said, we've been in this room or
2 a similar room and discussed heterozygous FH and
3 diagnostic genetic tests for that condition. And
4 we have a similar problem with multiple mutations,
5 undiscovered mutations, and it is extremely
6 cumbersome for clinicians to use that kind of
7 genetic data to actually make a decision and then
8 frankly to get it through the various payment
9 mechanisms to get the drug for the patients who
10 they strongly feel needed.

11 So I would be reluctant to require a genetic
12 test as part of the labeling because, even if it's
13 a suggestion, it ends up being picked up by the
14 payors and ends up becoming sort of the de facto
15 rule because the drug, I anticipate, will be
16 expensive.

17 So lastly, I think the REMS is a key part of
18 the safety monitoring because I think the data that
19 we have from the open-label extension is
20 essentially biased because the enrollment into that
21 study is amongst people who did well when getting
22 the drug in the first trial.

1 So we're not getting an adequate sense of
2 what the true risks and benefits are in that
3 particular population. That's a population who
4 tolerates the drug and is interested in getting it
5 going forward. So with that, I'll stop.

6 DR. WILSON: So if I could jump in,
7 Dr. Newman, you have to go, so can we have you vote
8 next?

9 DR. NEWMAN: Thank you. This was a very
10 difficult decision for me because I know how
11 difficult life is for patients with familial
12 chylomicronemia syndrome. But I looked at the
13 question literally, which is, has the applicant
14 provided sufficient efficacy and safety data to
15 support approval of volanesorsen.

16 I felt that, although there was a
17 significant reduction in triglycerides with the
18 dose used, which may not be the dose used in
19 clinical practice, that there was no clinical
20 benefit on either pancreatitis, abdominal pain, or
21 on any other symptoms and signs that these patients
22 might have. But my real concern was the benefit-

1 risk ratio.

2 I thought that the risk was too severe, the
3 risk of bleeding, obviously. And this may not be
4 predictable in certain instances and it could cause
5 a life-threatening bleed.

6 So I also thought that the dosing regimen
7 that is going to be used has not been adequately
8 studied, so therefore, we can't really evaluate the
9 benefit-risk and know how effective it is in
10 reducing triglycerides and whether it would
11 mitigate the risk of thrombocytopenia and bleeding.

12 But I think that, had the question been
13 different, I might have voted a different way
14 because there is a need for this drug, but I didn't
15 take that into consideration in my answer. And I
16 think that more efficacy and safety data would be
17 extremely helpful and I think we need more placebo-
18 controlled trials using the new dosing and platelet
19 monitoring regimen and a particular emphasis on
20 safety for longer periods.

21 So that explains my vote.

22 DR. WILSON: Before you go, please state

1 your name and how you voted for the record. Thank
2 you.

3 DR. NEWMAN: My name is Connie Newman and I
4 voted no.

5 DR. STRONCEK: I'm Dave Stroncek and I voted
6 yes. The data shows that the drug is effective for
7 lowering triglycerides. The safety profile of the
8 drug, though, is very problematic, not only the
9 thrombocytopenia, risk of bleeding, but the risk of
10 serum sickness, hypersensitivity, and skin
11 reactions.

12 Despite this, I voted yes because there's no
13 other treatment available for this patient
14 population. I think, though, because of all the
15 safety concerns, it is critical to move forward
16 with a robust risk mitigation strategy, which would
17 include biweekly platelet counts or platelet tests.
18 I think it's also important to encourage data
19 collection and data analysis in further studies so
20 the whole list of questions that we're all asking
21 can maybe be addressed in the future.

22 DR. WEBER: This is Tom Weber. I voted no.

1 Again, I'll try to be brief. I think it's been
2 stated this is a significant and serious condition
3 with potentially life-threatening complications as
4 pancreatitis.

5 It was a difficult decision for me, but
6 again, I try to balance risk and benefit in the
7 nature of the question that was asked. And I had
8 some concerns. I think specifically I had concerns
9 about the study population that was included in the
10 trial and may not have represented the real-world
11 experience of this and, even though it met the
12 primary endpoint, didn't show at least in the
13 concern in terms of improvements and concerns over
14 pancreatitis or some of the GI symptoms.

15 I also have concerns about the frequency of
16 thrombocytopenia in the study and don't believe at
17 this point that a REMS program can anticipate or
18 identify the more idiosyncratic events that can
19 occur, so there's a particular concern there.

20 More minor but still concerning is the rate
21 of cutaneous events, and hypersensitivity, and also
22 GI, liver-related events. And that may be

1 reflective of the underlying PK of the drug, which
2 we know accumulates to a greater degree within the
3 liver.

4 Then probably most importantly, the efficacy
5 as proposed for the treatment strategy based on
6 weight and based on every-other-week dosing really
7 hasn't been proven and I don't think warrants
8 approval of the drug.

9 The data was encouraging in terms of the
10 dose adjustments, but that wasn't the way that the
11 study was set up, so I'm concerned about that. As
12 far as where to go from here, I think that studying
13 it in a more defined fashion in terms of every-
14 other-week dosing or perhaps reduced dosing of 200
15 milligrams weekly, which in the phase 2 trials did
16 show very good efficacy with regard to triglyceride
17 lowering, would be a good step.

18 The other thing that I came away from the
19 data is that it looked like the thrombocytopenia
20 events occurred primarily after 90 days, not
21 necessarily some of the idiosyncratic events, but
22 perhaps intermittent dosing of 3 months on,

1 3 months off because the long half-life of the drug
2 could be an approach that may be safer for a
3 lifelong therapy where there are still serious
4 concerns.

5 As far as identifying subjects or patients
6 for this that are stratifying, there's a recent
7 review of this condition, of FCS, and perhaps
8 trying to define it separately from familial
9 combined hyperlipidemia with apoB testing, which is
10 commercially available.

11 So some other things can be done to try to
12 better define a population, I think, and who is
13 going to benefit from this therapy.

14 DR. LOW WANG: My name is Cecelia Low Wang
15 and I voted yes. This was really because I think
16 the sponsor has demonstrated marked triglyceride
17 lowering and I was encouraged by the fact that
18 there was no major bleeding, although there was 1
19 patient with platelet count of less than 10,000.

20 There are no other effective therapies and I
21 really wanted to make sure that there was access to
22 therapy for this rare and debilitating disorder.

1 Just a few points; just in terms of
2 balancing benefits and risks, I do think that the
3 indication for the drug should be patients with FCS
4 with quality of life significantly affected by the
5 hypertriglyceridemia. That could include
6 pancreatitis within the past year.

7 Also, I think the current dosing proposal
8 and monitoring is reasonable, but will not prevent
9 type 2 thrombocytopenia, as mentioned before. I
10 was very impressed by the REMS proposal that was
11 proposed by the sponsor. And I hope that can be
12 done.

13 I think that the label needs to include some
14 type of warning about concomitant antiplatelet or
15 anticoagulant therapies and the need for renal
16 function monitoring and proteinuria monitoring.

17 As has been mentioned, I think that there
18 are a number of studies that need to be done. And
19 so there's a lot of information that we're still
20 missing, requiring a post-marketing study with a
21 hard deadline in a selected population of patients
22 to better assess the safety profile, including the

1 hypersensitivity reactions using bleeding as a
2 safety endpoint.

3 Looking at platelet function, quality of
4 life measures, trying to decrease the injection
5 site reactions, trying to figure out the mechanisms
6 for the thrombocytopenia and trying to figure out
7 what's happening with the platelet function.

8 But I do think that this is life changing in
9 select patients, as I mentioned before, and this is
10 why I voted yes, but we need a lot more
11 information.

12 DR. NEATON: Jim Neaton. I voted no. So I
13 think potential benefit of this drug could be
14 large, but the realized benefit is uncertain.
15 There are some major safety concerns and our
16 ability to mitigate those safety issues is also an
17 uncertainty.

18 When I look at overall risk-benefit, it
19 doesn't seem to stand up and, when I look at the
20 patient dropout in the study and the number or
21 percent that went onto open label, then dropped out
22 in open label, I think the study participants are

1 telling us that.

2 Now, I thought about voting yes and
3 recommending a different high-risk population. I
4 guess that was an option as well. But then we
5 don't have the data on risk-benefit for that
6 population.

7 So I'm left with kind of a recommendation
8 that this potentially is a very good drug, but it
9 should be studied in a much higher-risk population
10 given the known risk.

11 DR. SINCLAIR: Hi I'm Susan Sinclair and I
12 voted no. I would have liked to have voted yes,
13 but I took the question literally as well with
14 sufficient efficacy and safety data presented.
15 Efficacy was certainly impressive for the surrogate
16 endpoint, but I did not see clinical benefit beyond
17 surrogate endpoint.

18 Also, the REMS cannot adequately mitigate
19 the risks of the unpredictable decreases in
20 platelet count. And the high discontinuations
21 again suggest some sort of perhaps unmeasured
22 satisfaction.

1 The pre-market signals of course bothered me
2 the most, but I do know that there's being data
3 collected as we speak, so I'm hopeful that, that
4 will shine some light on this potential signal and
5 that something can be approved for this population,
6 but based on the question, I voted no.

7 **Adjournment**

8 DR. WILSON: We're about done. We give the
9 last word to the FDA. Any comments from our FDA
10 leadership?

11 DR. SMITH: I think I have no additional
12 comments. I'd like to thank you all for a very
13 robust discussion today. It was incredibly helpful
14 for us.

15 I think, even the questions that we skipped
16 over, you were able to work in comments. So that's
17 helpful. As you got a sense, this has been a very
18 challenging application for us and we get that it
19 was not easy for you, either. So we have something
20 in common.

21 So thank you all very, very much for your
22 time and we'll see you next time.

1 (Whereupon, at 5:34 p.m., the meeting was
2 adjourned.)
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